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Jonathan L. Benumof, MD, *Consulting Editor*

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INFECTION IN ANESTHESIA

Arnold J. Berry, MD, *Guest Editor*

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| Infectious agents can be transmitted between patients, anesthesia personnel, and equipment. Anesthesia departments should have infection control policies to assure that patients do not acquire infections during their anesthesia care and to protect personnel from occupationally acquired infections. "Universal precautions" have been recommended as strategies against occupational transmission of blood-borne infections to health care workers. |                          |
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ARNOLD J. BERRY, M.D.  
*Guest Editor*

## *Preface*

Although it has been recognized for several decades that some patients carry infectious agents that may be transmitted to anesthesia personnel in the operating room, it is the AIDS epidemic that has only recently caused physicians to examine their infection control policies more closely. Herpetic whitlow, a herpes viral infection of the fingers, was reported in anesthesiologists in the 1970s as a result of contacting oral secretions of infected patients, and recommendations were made at that time for the use of gloves during placement of endotracheal tubes and pharyngeal suctioning. This was not emphasized during my residency training and the routine use of gloves when contacting patient's body fluids was not incorporated into my practice until the 1980s when I became interested in the transmission of blood-borne infections in the operating room. Now the use of gloves has become part of the Centers for Disease Control's "universal precautions," strategies to prevent occupational transmission of blood-borne infections to health care workers. The Occupational Safety and Health Administration has determined that some health care workers are at a significant health risk as the result of occupational exposure to blood that may carry disease-producing organisms, and by authority of the Occupational Safety and Health Act of 1970, it is now proposing Federal standards to minimize these hazards. Infection control practices will have gone from the early unheeded recommendations in the medical literature to federally mandated practice standards.

Patients coming for surgery are asking us if they will receive blood or blood products during their procedure and what is the associated risk of infection. The press has made the public aware of transfusion-transmitted infections, especially hepatitis and human immunodeficiency virus. Anesthesiologists make up the single largest specialty group responsible for transfusions, and therefore, they must be familiar with the current data in order to make informed decisions on transfusion practices.

As we have become more aware that patients may carry infectious agents, anesthesiologists are concerned that equipment contaminated during the care of patients may transmit the infection to others. Disinfection policies and routines for handling equipment are being reassessed in light of current information about blood-borne infections.

Because a larger number of healthy patients are having operative procedures on an outpatient basis, hospitalized surgical patients are more likely to have multiple medical problems including infectious processes. Additionally, critically ill patients are especially at risk for nosocomially acquired infections. Anesthesiologists must understand the anesthetic implications of these infections and the current antibiotics used to treat them.

Each section of this issue is a timely review of current information that I believe will impact on your practice. It has not been possible to cover all areas related to infection in anesthesia extensively because of the size limitations of this book, so topics most relevant to clinical anesthesia have been chosen. The contributors to this issue have all been selected because of their recognized expertise. I deeply appreciate the efforts of the contributing authors and the assistance of the publisher.

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## **Foreword**

Awareness of the impact of the blood-borne infections, hepatitis B, and AIDS, has prompted health care personnel to examine their role both in the transmission of disease to patients and their risk of being infected by organisms carried by patients. However, anesthesia personnel are often not fully cognizant of their role in transmitting infections to and acquiring infections from patients because of their short contact with them in the operating room, the sequelae of infectious processes are delayed, and lack of follow-up after the surgical procedure. Thus, it is appropriate to ask (and this issue of *Anesthesiology Clinics of North America* answers) what are appropriate disinfection procedures for anesthesia equipment after use on patients with blood-borne infections? Does this differ from routine cleaning procedures? Does anesthesia equipment require special handling before use on immunosuppressed patients? What are current guidelines on the use of central venous catheters that have been in place for several days? Should they be changed on a regular basis, and are multi-lumen catheters a greater risk for infection than those with a single lumen?

There are many other vitally important issues concerning infection in anesthesia. What are the human immunodeficiency virus infection (AIDS) and viral hepatitis all about? The risk of transmitting infection from the blood supply of the United States has now been evaluated and patients will increasingly and appropriately demand to be expertly informed of their risk of hepatitis or AIDS with intra-operative transfusion. How does anesthesia and surgery alter a patient immunologically, and how does sepsis alter patient physiology? Perioperative nosocomial pneumonia may be caused by alteration of the normal distribution of bacterial flora due to many extrinsic sources, including the anesthesiologist. For those anesthesiologists caring for patients in intensive care units, they must know about the new antibiotics. Likewise, anesthesiologists must know what the current rec-

ommendations for subacute bacterial endocarditis prophylaxis are for patients with cardiac lesions.

Finally, there are pressing concerns of occupational danger and risk of the anesthesiologist becoming infected. How should the concept of "universal precautions" be adapted into the practice of anesthesia? What should you do if you stick yourself with a needle? Who should receive the hepatitis B vaccine and what are the associated risks? What is the responsibility of the hospital or department or government to protect and educate anesthesia personnel about their risk of occupationally transmitted infections?

Dr. Arnold Berry has long been interested in this area of anesthesia, and based on his previous research, publications, lectures, and ongoing administrative work, is eminently qualified to guest edit this issue of *Anesthesiology Clinics of North America* on Infection in Anesthesia. For example, he has been a principal investigator for a series of studies on the epidemiology of hepatitis B in physician anesthesiologists, certified registered nurse anesthetists, and anesthesia residents in conjunction with the Centers for Disease Control. He has authored important reviews on occupational hazards for anesthesia personnel, as well as advisories in the American Society of Anesthesiologists' newsletter on "Blood-borne Infections." Finally, he is a member of the American Society of Anesthesiologists' Committee on Health of Operating Room Personnel and the Emory University Hospital Infection Control Committee. The authors he has chosen for the specific articles are all recognized experts and come from numerous disciplines, which appropriately reflects the broad implications of infection. In view of the seriousness, and to a significant extent, the preventable nature of infection, and the acknowledged expertise of the authors and editor, the practice of all anesthesiologists will benefit by the reading of this issue of *Anesthesiology Clinics of North America*.

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## FORTHCOMING ISSUES

March 1990

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Laurence S. Reisner, MD, *Guest Editor*

Obstetric anesthesia in the United States has undergone an exciting evolution through the last three decades. Indeed, the anesthesiologist is now considered by all who deal with the parturient patient to be an essential member of the obstetric care team. This issue is a timely update and perspective on maternal and fetal physiology, obstetric anesthesia, and the effects of anesthesia on both of these patients, and perinatal medicine; the book is authored by experts actively involved in all aspects of obstetric anesthesia.

June 1990

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Gerald Shapiro, MD, MPA, *Guest Editor*

September 1990

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Bruce Spiess, MD, *Guest Editor*

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A. Scott Wheeler, MD, *Guest Editor*

June 1989

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Stephen Thomas, MD, *Guest Editor*

March 1989

### **MANAGEMENT OF POSTOPERATIVE PAIN**

Rollin V. Oden, MD, *Guest Editor*

December 1988

### **CARDIAC MONITORING**

Paul G. Barash, MD, *Guest Editor*

## Community-Acquired Respiratory Tract Infections

*Eric G. Honig, MD\**

Community-acquired lower respiratory tract infections are extremely common and economically costly problems with a potentially significant morbidity and mortality. It is estimated that there are 200 million community-acquired respiratory tract infections in the United States per year. This figure is probably an underestimate because most community-acquired respiratory infections are not reported to public health authorities.

Upper respiratory tract infections are the commonest complaints bringing patients to medical attention. For every case of pneumonia, there are 33.1 cases of influenza, 27.6 common colds, and 1.9 cases of bronchitis. There are perhaps 3.3 million cases of pneumonia annually or 2 per cent of the population per year. Most community-acquired pneumonias are nonbacterial and may be adequately managed on an outpatient basis, but about 500,000 pneumonia patients require hospitalization each year, with a 10 to 15 per cent case fatality rate.<sup>25, 50</sup> Community-acquired pneumonias represent approximately 9 per cent of medical admissions to a general hospital.<sup>152</sup> They are the sixth most common cause of death in the United States, fourth among the elderly and the single most common infectious cause of death.<sup>25, 162</sup>

### DEFENSES

The respiratory system possesses an effective set of defenses against microbial invaders.<sup>136, 137</sup> The nasopharynx, mucociliary system, bronchial musculature, and secretory IgA all effectively prevent microbes from gaining access to the airspaces. The alveolar space is additionally protected by cellular elements, macrophages, lymphocytes, and neutrophils, as well as humoral elements such as the complement pathway, IgG, and transferrin.

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Microbes can gain access to the respiratory tract by inhalation of infectious aerosols, aspiration of colonized mouth flora, by hematogenous spread from a remote soft-tissue focus, or by contiguous spread from the chest or abdomen. Normally only a large inoculum or an especially virulent pathogen is capable of overcoming these defenses, but when they are compromised by systemic or respiratory tract disease, potential pathogens may gain access to the respiratory tract.

## PATHOGENESIS

### Upper Respiratory Tract

Upper respiratory tract infections are usually associated with pathogens of high virulence and usually do not involve defects in respiratory defenses.<sup>64</sup> The major findings of upper respiratory tract infections are the consequence of inflammation and edema of upper airway structures with their consequent narrowing. Airway resistance and work of breathing is increased. In the more severe cases, the work of breathing may be sufficiently high to precipitate respiratory muscle fatigue and respiratory failure. The increased inspiratory effort may result in wide pressure swings in the thorax and can lead to pulmonary edema, especially in children. Involvement of the bronchial tree may adversely affect ventilation-perfusion balance in the lung and lead to hypoxemia, which is usually relatively mild and oxygen responsive. The location of the narrowing differentiates among the major clinical entities. Hoarseness points to laryngeal disease. Stridor localizes the site of narrowing to the extrathoracic airway, whereas wheezing suggests narrowing distal to the thoracic inlet. Cough originates from disease of the larynx and beyond.

### Lower Respiratory Tract

**Predisposing Risks.** With the exception of significant pathogens such as *Streptococcus pneumoniae*, *Mycoplasma pneumoniae* and *vir*, significant lower respiratory tract infections are uncommon in the normal host. Most lower respiratory tract infections are associated with significant compromise of the systemic or local defenses. Advanced age, nursing home placement with prior antibiotic therapy,<sup>49</sup> and ethanolism all predispose to increased oropharyngeal bacterial colonization, especially with gram-negative bacilli. Alterations of consciousness due to neurologic disease or to substance abuse may predispose to repeated aspiration. Cigarette smoking and chronic airway disease may interfere with the effectiveness of the mucociliary escalator. Diabetes mellitus interferes with effectiveness of cellular defenses.<sup>20, 79, 93</sup> Nonsteroidal anti-inflammatory drugs have been shown to decrease ciliary motility and interfere with neutrophilic chemotactic factor.<sup>52</sup>

## AIRWAY INFECTION

In bronchitis and bronchiolitis, organisms attack the ciliated columnar epithelium of the respiratory tract leading to ciliostasis, necrosis, and slough of airway epithelium. Inflammation and edema along with retained secretions narrow the diameter of the airways, increasing airway resistance and creating the cardinal symptom of cough and signs of wheezes and rhonchi. Inflammation and cough typically lead to burning midsternal chest pain. Airway narrowing also impairs ventilation-perfusion matching in the airspaces leading to hypoxemia.

Because the majority of airflow resistance in young children is located in peripheral small airways, bronchitis and bronchiolitis can be particularly serious. Pediatric bronchiolitis presents as severe hyperinflation with airflow limitation. Hypoxemia is present, as is the risk of respiratory failure.<sup>63</sup> Because viral respiratory tract infections impair the mucociliary escalator and the effectiveness of the cellular respiratory defenses, bacterial superinfections are a common complication.<sup>136-138</sup>

## AIR-SPACE DISEASE (PNEUMONIA)

Pneumonia is associated with a cellular inflammatory exudate in the alveolar space with alveolar and interstitial edema. The fluid and exudate make the affected lung stiffer, increasing the work of breathing, and leading to a respiratory pattern of rapid, shallow breaths. Closure of distal lung units leads to inspiratory rales and a shunt physiology characterized by profound hypoxemia with a poor response to supplemental oxygen. The largest group of deaths by pneumonia occur in the first 72 hours of illness and are due to refractory hypoxemia or to sepsis. Late deaths are often attributable to extrapulmonary infection, superinfection, or multiple organ failure. The hypoxemia of pneumonia may be prolonged.<sup>20, 33, 97</sup>

## APPROACH TO THE PATIENT

Most community-acquired respiratory tract infections are mild self-limited illnesses, but the physician must be prepared to deal promptly and effectively with life-threatening infections. Often, the diagnosis must be made and treatment initiated before definitive microbiologic information is available. Knowledge of the differential diagnosis, the pathogens most likely to be involved, and the potential risk to the patient are essential. Upper respiratory tract infections are characterized by the prominence of hoarseness and sore throat, with a relative absence of signs and symptoms referable to the chest. Nasal

and sinus complaints are often present and stridor is a specific finding. Rales and consolidation are notably absent on examination of the chest. The chest roentgenogram shows few acute abnormalities. Lower respiratory tract infections present with cough and dyspnea. Wheezing, rales, and consolidation point specifically to the lower respiratory tract. Although upper airway signs and symptoms may be present, the more severe complaints are directed toward the airways and pulmonary parenchyma. In airspace infections, the chest roentgenogram is by definition abnormal.

### Upper Airway Infections

In cases of upper airway infection, the clinician must take two issues into account: the potential of the illness to cause significant airway compromise, and the likelihood of a bacterial etiology, determining the utility of specific antibiotic therapy.

The presence of dyspnea out of proportion to pharyngeal findings and stridor suggest epiglottitis or bacterial tracheitis, life-threatening bacterial infections that may cause significant airway obstruction.<sup>55</sup> Securing the airway and specific antibiotic therapy are essential in these cases. Careful examination of the pharyngeal cavity and posteroanterior and lateral soft-tissue roentgenograms of the neck are helpful initial steps, but most often, prompt endoscopic visualization of the supraglottic space and larynx are necessary. Direct visualization carries some risk of exacerbating airway obstruction and should be performed in the presence of a physician skilled in airway management with facilities for emergency intubation or tracheostomy if needed. Cultures and gram stains of airway secretions are appropriate.

In the absence of severe supraglottic disease, croup can be diagnosed by its characteristic barking cough with pharyngitis on clinical examination. The management of croup is largely supportive, but patients should be observed closely for the possible development of respiratory failure. In pharyngitis, the major issue is the identification and treatment of infection due to group A beta-hemolytic streptococcus (GABHS) and the avoidance of its immunologic sequelae, rheumatic fever and streptococcal glomerulonephritis. Throat cultures are necessary and antistreptococcal therapy should be initiated pending culture results.

### Lower Respiratory Tract

Lower respiratory tract infections should initially be categorized as airway or airspace infections by the presence or absence of rales and consolidation, sputum production, fever, and the absence of rhinorrhea.<sup>6</sup> In the absence of chest findings, bronchitis or bronchiolitis are more likely. Bronchodilator therapy and symptomatic cough management are helpful and antibiotic therapy is of limited utility. Chest roentgenography is usually not of value in airway infections.<sup>56</sup>

Pneumonia, infection of the alveolar airspaces, should first be judged as acute, subacute, or chronic. A duration of respiratory illness measured in weeks to months should raise suspicion for tuberculosis

or mycobacteriosis. A tuberculin skin test should be applied (unless there is a prior history of tuberculin reactivity), and sputum collected for mycobacterial cultures and acid-fast staining. A chest roentgenogram should be obtained. The presence of acid-fast bacilli on smear, or productive cough with strong clinical suspicion for tuberculosis mandates isolation until smear negativity is achieved or 2-week antituberculous therapy is completed. All active cases should be reported to local public health departments and close contacts should receive skin testing. The need for hospitalization in active tuberculosis should be determined by the patient's overall clinical condition and home situation rather than the presence of the disease only.<sup>15, 23, 60</sup>

In pneumonia, essential information includes the history and physical examination, chest roentgenogram, arterial blood gases, blood cultures, and culture and examination of the sputum. The clinician should first assess the severity of the illness and the need for hospitalization and intensive therapy. Patients over the age of 60 who present with confusion, a respiratory rate over 30 breaths per minute, a diastolic blood pressure below 60 mm Hg, azotemia, malnutrition defined as an albumin below 3.5 g per dl, or multilobe involvement represent a high risk for mortality. A white blood cell count less than 4000 per mm<sup>3</sup> or greater than 30,000 per mm<sup>3</sup> represents an additional risk factor. Mortality has been shown to correlate with respiratory rate, and a rate greater than 44 per minute carries nearly a 100 per cent risk of death. These patients should be hospitalized immediately, observed closely, and treated as intensively as possible.<sup>20, 123, 131, 156</sup>

Patients under the age of 50 who have only a single lobe involved, a respiratory rate below 25 breaths per minute, a pulse under 100 beats per minute, a PaO<sub>2</sub> greater than 60 mm Hg, and no significant complicating illnesses may be treated safely as outpatients.<sup>84, 143</sup>

Definitive antibiotic therapy should be initiated as quickly as possible for all patients with pneumonia.<sup>20, 97</sup> Culture material will not be available in sufficient time to guide therapy, but gram staining of an adequate sputum will often provide definitive information. Sputum, however, may not always be available and is often of such poor quality as to provide more misinformation than guidance.<sup>66</sup> The physician should personally evaluate the quality of the sputum specimen before making an antibiotic choice based on a stained sputum specimen, and that choice must often be empiric. Once definitive microbiologic information becomes available, therapy may be changed if needed.<sup>48, 166</sup>

Community-acquired pneumonias may be classified on the basis of their presentation as typical or atypical. Typical pneumonias are usually bacterial. The clinical picture associated with the common infecting organisms is not sufficiently distinct to permit specific therapy on empiric grounds. Antibiotic therapy is selected to cover the organisms most likely to be encountered in the setting. Atypical pneumonias, because they are not associated with a diagnostic gram stain, are more difficult to approach. In some cases, such as varicella pneu-

monia, the presentation may be sufficiently distinctive so as to permit a specific diagnosis, and in others, the presence of ongoing epidemics in the community may allow a diagnosis to be inferred. In most instances, the diagnosis depends on specific serologic studies or cultures of respiratory tract material, and empiric therapy must be begun before this information is available.

## SPECIFIC INFECTIONS

### Upper Respiratory Tract

**Common Cold.** The common cold<sup>62</sup> is a distinctive self-limited viral upper respiratory tract infection characterized by a dry scratchy sore throat followed by a proteinaceous nasal discharge. Malaise, myalgias, and a low-grade temperature may be present. Treatment is symptomatic with nasal decongestants and cough suppressants such as dextromethorphan. Sympathomimetic nasal decongestants carry a risk of rebound mucosal edema if used for too long a period of time. The clinician should be alert to the possibility of significant complicating sinusitis or otitis media.

**Pharyngitis.** Pharyngitis<sup>64</sup> is characterized by a sore throat, odynophagia, malaise, and fever. It is almost always viral in origin in children, but is more likely to be bacterial in young adults.

The major concern in pharyngitis is for infection with GABHS and the potential for post-infectious streptococcal syndromes such as glomerulonephritis or rheumatic fever. The presence of a pharyngeal exudate is not pathognomonic for strep throat, but a beefy red pharynx with a yellowish exudate, palatal petechiae, and cervical lymphadenopathy are highly suggestive. Leukocytosis with a left shift is common. Throat cultures should be obtained and oral or intramuscular penicillin or erythromycin given while awaiting culture results.<sup>82</sup> Rapidly available serologic tests for the presence of GABHS may supplant the throat culture in the near future. Therapy may be continued based on culture results and the response to therapy. Splenomegaly with a grayish-white pharyngeal exudate suggests that a pharyngitis may be due to mononucleosis and infection with Epstein-Barr virus. A thick tenacious membrane suggests infection with *Corynebacterium diphtheriae*. Diphtheria may cause airway obstruction by distal progression of the membrane in 30 per cent of cases. When recognized, diphtheria should be treated by administration of antitoxin along with penicillin or erythromycin.<sup>125</sup>

Other causes of pharyngitis include mycoplasma pneumoniae, which is associated with a prominent cough, *Chlamydia*, herpesvirus, and the respiratory viruses. Gonococcal pharyngitis should be considered in sexually active patients and is treated with tetracycline or trimethoprim-sulfamethoxazole (TM-S).<sup>65, 125</sup>

**Epiglottitis.** Epiglottitis is a potentially life-threatening supraglottic upper airway infection associated with type b *Hemophilus in-*

*fluenzae*. It is characterized by a rapidly progressing picture of fever, sore throat, stridor, and the four Ds: dysphagia, dyspnea, dysphonia, and drooling.<sup>64, 135</sup> The peak incidence is among children aged 1 to 6 years but approximately 20 per cent of cases are in adults.<sup>105</sup> Acute epiglottitis evolves over a few hours. Patients typically present sitting anxiously upright, leaning forward, and drooling. There is hoarseness and stridor but no cough. Tachypnea and tachycardia are present, and hypoxia suggests either airspace involvement or pulmonary edema due to the wide swings in respiratory pressures.<sup>29</sup> The epiglottis is beefy, angry red, and swollen. Thick secretions may be present.

The clinical impression of epiglottitis is best confirmed by direct pharyngoscopy. Extreme caution must be used in direct examination of the airway as even minimal contact with the epiglottis may precipitate acute airway obstruction and asphyxia. A physician with experience in airway management should be immediately available. Usually direct visualization of the larynx is performed only in the operating room where emergency airway management can more easily take place.<sup>35</sup> Lateral soft-tissue films of the neck show marked enlargement of the epiglottis to more than 8 mm with obliteration of the vallecular folds, the so-called "thumbprint sign."<sup>135, 140</sup> The first priority is to secure the airway. Acute upper airway obstruction is usually not total and can be successfully managed by assisting ventilation via face mask. Patients with severe epiglottitis should be intubated in the operating room. Tracheostomy may be necessary. Patients first seen within 8 hours of the beginning of the episode appear to be at particular risk for respiratory failure.<sup>105</sup> Adequate supplemental O<sub>2</sub> is obligatory. Once the airway is secured, definitive antibiotic therapy should be instituted with ampicillin, a second generation cephalosporin, or chloramphenicol to cover beta-lactamase producing strains of *Hemophilus*. The patient should remain intubated until there is evidence of resolution of the supraglottic edema, usually in 1 to 3 days. Antibiotics should be continued for 7 to 10 days. Four days of rifampin are suggested for household contacts, carriers, and patients recovering from epiglottitis to reduce the carrier rate.<sup>35</sup>

**Laryngotracheobronchitis.** Laryngotracheobronchitis is an upper respiratory infection caused by parainfluenzavirus, respiratory syncytial virus, and occasionally mycoplasma, characterized by fever, dyspnea, hoarseness, and stridor accompanied by a characteristic brassy barking cough. Laryngotracheobronchitis is most common in children between the ages of 3 months and 3 years in whom it is associated with the croup syndrome.<sup>32, 64, 117</sup>

Pediatric croup results from narrowing of the small subglottic airway at the level of the cricoid cartilage. Diagnosis of croup is based on the characteristic hoarseness, stridor, and cough. Croup can be distinguished from epiglottitis by its subacute presentation and characteristic cough. A posteroanterior view of the soft tissues of the neck may be helpful by revealing subglottic narrowing of the air column, the "church steeple" sign.<sup>35, 135</sup> Serologic identification of the responsible organism is rarely helpful.

The goal of therapy is the relief of upper airway obstruction by reduction of airway edema. Cooling the airway by inhaling a mist of cool dry air is particularly effective. Cool moist air may help loosen dried secretions, but warm moist air should be avoided. Inhaled alpha-agonists such as phenylephrine or racemic epinephrine may be helpful, but are short acting and carry a risk of rebound edema between treatments. The role of steroids is questionable. There is no evidence that antibiotics are helpful in croup. Croup usually resolves in 3 to 5 days. Reactive airways may be a consequence.<sup>2, 32</sup>

**Bacterial Tracheitis.** Bacterial tracheitis<sup>22, 64, 73, 146</sup> is a severe, sometimes life-threatening upper airway infection. It is most commonly caused by *Staphylococcus aureus*, beta-hemolytic *Streptococcus*, or *Haemophilus influenzae*. It is seen in older children and adults who present with a croup-like syndrome accompanied by large amounts of purulent sputum. Airway distress results from the large amount of secretions that may obstruct the airway. Fever and stridor may be present. There is no response to aerosol therapy. Lateral soft-tissue views of the neck may help differentiate tracheitis from croup or epiglottitis by showing normal supraglottic and subglottic spaces with clouding of the tracheal air column. Direct endoscopic visualization is diagnostic.<sup>32</sup> Intubation is often required, and a contiguous pneumonia may be present in more than half the cases. Antibiotics should be prescribed to cover *Staphylococcus*.

## AIRWAYS DISEASES

### Acute Bronchitis

Acute bronchitis is a lower respiratory tract condition characterized by a cough, usually without fever, seen in the absence of an upper respiratory tract infection. Acute bronchitis presents as the sudden onset of a new cough that may or may not be productive of sputum.

Acute bronchitis is caused by many of the same organisms as upper respiratory tract infections and are often viral. Bronchitic infections are most often seen in winter although they may occur year-round and in epidemics. Seasonal tendencies can give a clue as to the identity of the infectious agent. Late winter and early spring infections are more likely to be caused by influenza virus, respiratory syncytial virus, or coronaviruses. Summer bronchitis is most commonly associated with enteroviruses. In the fall months, parainfluenza and rhinoviruses are common. Bronchitis with fever is attributed to adenovirus, influenza virus, or mycoplasma.<sup>9, 54, 56, 61, 115, 130</sup>

*Mycoplasma pneumoniae* is far more likely to produce bronchitis than pneumonia and is a common form of bronchitis.<sup>24, 28</sup> Pontiac fever is an unusual form of bronchitis caused by *Legionella pneumophila* and should be considered in the differential diagnosis of warm season bronchitis. It is associated with fever, headache, and myalgias.<sup>34</sup>

**Signs and Symptoms.** The major presenting symptom of acute

bronchitis is a cough that may be dry, mucoid, or mucopurulent. Patients may experience substernal and sometimes burning chest pain with a deep breath or cough. There are no acute infiltrates on chest roentgenogram and no physical findings for consolidation.

**Management.** Erythromycin is indicated in the management of mycoplasma bronchitis or Pontiac fever, but otherwise neither chest films nor antibiotics are necessary. The best treatment is usually symptomatic. Dextromethorphan or codeine may be helpful for the cough.

Because the bronchial epithelium is disrupted, prolonged increases in airway reactivity and frank asthma may be seen after an episode of acute bronchitis. Some childhood asthma may represent sequelae of a bronchitic episode. Bacterial superinfection may occur.

### Chronic Bronchitis

Chronic bronchitis is a disease of smokers defined by the American Thoracic Society<sup>4</sup> as a productive cough most days of the week for at least 3 consecutive months and 2 consecutive years and is usually associated with emphysema or chronic obstructive pulmonary disease (COPD).<sup>54, 56</sup>

**Etiologic Agents.** Exacerbations of chronic bronchitis occurring during winter months tend to be viral, whereas those in warmer months are more often bacterial. Rhinovirus and respiratory syncytial virus are often implicated in viral exacerbations whereas *Streptococcus pneumoniae* and *Hemophilus influenzae* are recovered in 80 per cent of transtracheal aspirates in bacterial exacerbations. Mycoplasma is a frequent offender and *Branhamella catarrhalis* has recently been recognized as a significant pathogen as well.<sup>118</sup> Response to antibiotic therapy is in large part determined by how characteristic the presentation is for a bacterial infection.<sup>51, 38</sup>

**Signs and Symptoms.** Exacerbations of chronic bronchitis are characterized by a worsening cough, increased dyspnea, change in cough, increasing sputum volume, and purulence. Physical examination reveals an increased respiratory rate in 40 per cent of patients. Fever and tachycardia are present in one third or less. Exacerbations of chronic bronchitis carry a risk of respiratory failure.<sup>5</sup>

The diagnosis of an exacerbation of chronic bronchitis is made by clinical history. When a bacterial etiology is suspected, antibiotic selection should be appropriate for *Pneumococcus* and *Hemophilus*. Useful agents include tetracycline/doxycycline, ampicillin/amoxicillin, TM-S, oral cephalosporins, and the quinolones. Theophyllines, beta-adrenergic and anticholinergic bronchodilators are often helpful and supplemental oxygen may be necessary. Although the role of corticosteroids in exacerbations of chronic bronchitis is controversial, they probably provide some benefit in hospitalized patients.<sup>5, 119, 139</sup>

The best care may be preventive with an emphasis on smoking cessation. Annual influenza vaccination should be administered to all patients with COPD. The benefit from pneumococcal vaccine is less well established but is currently recommended.<sup>7, 26, 41, 84</sup>

## Bronchiolitis

Bronchiolitis is a severe respiratory illness in children that may have significant sequelae. It is most commonly seen in the first 2 years of life. Respiratory syncytial virus is the commonest cause, but parainfluenzavirus and mycoplasma are also potential pathogens.

**Signs and Symptoms.** Bronchiolitis presents in children as an acute febrile illness with airway obstruction, hyperinflation, and respiratory distress. Physical findings include wheezing, grunting, cough, rib retraction, tachypnea, hypoxemia, and cyanosis. The illness lasts about 7 to 10 days.

**Management.** The most important therapeutic intervention is provision of adequate supplemental oxygen to keep the  $\text{PaO}_2$  above 60 mm Hg.

Antibiotics, corticosteroids, and bronchodilators have not been shown to be of any benefit. Aerosolized ribavirin may be helpful in severe cases.<sup>63</sup>

Adult bronchiolitis is usually a milder disease with a presentation similar to acute bronchitis. In adults, bronchiolitis presents with wheezing, fever, and mucopurulent cough. Reticulonodular infiltrates may be seen on the chest roentgenogram. *Streptococcus pneumoniae*, *Hemophilus*, and *Mycoplasma* are the most commonly reported causes.<sup>9, 31</sup>

## AIRSPACE INFECTIONS

Pneumonia is characterized by a cough, often productive, and is usually accompanied by fever. Infiltrates are present on the chest film.<sup>20, 85</sup>

**Table 1. Community-Acquired Pneumonia: Incidence and Etiology from 1971 to 1988**

| AUTHOR<br>REFERENCE      | FEKETY<br>43 | SULLIVAN<br>152 | DORFF<br>37 | WHITE<br>165 | MacFARLANE<br>99 | PROUT<br>133 | KLIMEK<br>81 |
|--------------------------|--------------|-----------------|-------------|--------------|------------------|--------------|--------------|
| COUNTRY                  | US           | US              | US          | UK           | UK               | SOUTH AFRICA | US           |
| YEAR                     | 1971         | 1972            | 1973        | 1981         | 1982             | 1983         | 1983         |
| NUMBER                   | 100          | 292             | 148         | 210          | 127              | 81           | 204          |
| Bacterial                | 66           | 167             | 111         | 43           | 123              | 30           | 204          |
| <i>Strep pneumoniae</i>  | 62           | 103             | 79          | 24           | 96               | 13           | 204          |
| <i>Haemophilus</i>       |              | 14              | 4           | 4            | 4                | 4            | 74           |
| <i>Staphylococcus</i>    | 1            | 17              | 11          | 8            | 3                |              | 31           |
| <i>Branhamella</i>       |              |                 |             |              |                  |              | 16           |
| <i>Legionella</i>        |              |                 |             | 3            | 19               | 1            |              |
| Anaerobes                |              |                 | 3           |              |                  |              | 28           |
| Gram negative            | 2            | 33              | 14          | 3            | 1                | 3            | 8            |
| Atypical                 |              | 43              | 12          | 70           | 21               | 8            | 45           |
| Mycoplasma               |              | 2               | 5           | 30           | 3                | 4            |              |
| Viri                     |              | 41              | 7           | 31           | 11               | 4            |              |
| <i>Coxiella burnetii</i> |              |                 |             | 6            | 1                |              |              |
| <i>Chlamydia</i>         |              |                 |             | 3            | 7                |              |              |
| Mixed infections         |              | 24              | 1           | 8            | 8                | 10           |              |
| No diagnosis             | 34           | 105             | 25          | 107          | 4                | 37           |              |

\* Outpatient series.

Pneumonia may be confused with congestive heart failure, lung cancer, pulmonary embolism, simple aspiration, the adult respiratory distress syndrome, or interstitial pulmonary fibrosis.<sup>79</sup>

The diagnosis may be particularly difficult in elderly patients whose presentation may be so subtle as to mislead the unwary physician. Fever, chills, cough, and chest pain may all be absent, and the patient may simply present with altered mental status, dehydration, loss of appetite, or inanition.<sup>57, 103, 109, 158</sup>

Although they are uncommon when considering all cases of pneumonia, certain organisms are more likely as pathogens in the presence of geographic or occupational risk factors. Melioidosis is more common among Southeast Asians, histoplasmosis in patients residing in the Ohio or Mississippi River valleys, and coccidioidomycosis in patients living or traveling in the San Joaquin Valley of California or Arizona.<sup>79</sup> Specific risk groups such as patients with AIDS have a characteristic set of infections. These are extensively reviewed elsewhere.<sup>111, 112, 150</sup>

Table 1 shows the causes of community-acquired pneumonias as reported in 15 series from 1971 to 1987.<sup>17, 18, 20, 37, 43, 69, 81, 85, 91, 99, 103, 106, 133, 152, 165</sup> These data suggest inpatient pneumonias tend to be bacterial whereas outpatient pneumonias are more commonly non-bacterial in origin.<sup>18</sup> In a large number of cases, no specific etiologic diagnosis can be made. A significant number of infections are of mixed etiology.<sup>21</sup> The lack of a specific diagnosis may be caused by failure to consider a specific organism, difficulties in obtaining timely serologic data, the uncertainty associated with sputum, the relative insensitivity of definitive culture sources such as blood and pleural fluid, and the suppressive effect of prior antibiotic therapy on culture material.<sup>13, 142, 147, 151, 154, 166</sup>

Table 1. (Continued)

| McNABB | LARSEN | BERNTSSON | MARRIE | BTS  | HOLMBERG | LEVY   | BERNTSSON* | TOTAL 14  |       |
|--------|--------|-----------|--------|------|----------|--------|------------|-----------|-------|
| 108.   | 85     | 17        | 103    | 20   | 69       | 91     | 18         | INPATIENT |       |
| UK     | US     | SWEDEN    | CANADA | UK   | SWEDEN   | FRANCE | SWEDEN     | SERIES    |       |
| 1984   | 1984   | 1985      | 1985   | 1987 | 1987     | 1988   | 1986       |           |       |
| 80     | 217    | 127       | 138    | 453  | 147      | 116    | 54         | 2440      | %     |
| 52     | 134    | 76        | 63     | 211  | 70       | 63     | 21         | 1413      | 57.91 |
| 40     | 52     | 69        | 13     | 154  | 57       | 30     | 9          | 866       | 61.29 |
| 5      | 19     | 5         | 13     | 26   | 8        | 13     | 12         | 150       | 10.62 |
| 3      | 18     | 1         | 4      | 4    | 1        | 3      |            | 90        | 6.37  |
|        |        |           |        |      | 3        | 1      |            | 4         | 0.28  |
| 1      | 8      | 1         | 1      | 9    | 4        | 5      |            | 80        | 5.66  |
|        | 23     |           | 20     |      |          | 3      |            | 57        | 4.03  |
| 1      | 6      |           | 4      | 4    |          | 8      |            | 124       | 8.78  |
| 5      | 12     | 44        | 31     | 116  | 25       | 10     | 47         | 397       | 16.27 |
|        | 10     | 18        | 1      | 81   | 7        | 4      | 37         | 165       | 41.56 |
| 5      | 2      | 23        | 23     | 32   | 16       | 5      | 14         | 200       | 50.38 |
|        |        |           | 1      | 5    |          |        |            | 13        | 3.27  |
|        |        | 3         | 6      | 13   | 2        | 1      | 4          | 35        | 8.82  |
| 16     |        | 22        | 19     | 17   | 15       | 13     | 12         | 153       | 6.27  |
| 29     | 102    | 27        | 61     | 150  | 43       | 35     | 41         | 759       | 31.11 |

## Signs and Symptoms

All pneumonias present with a characteristic set of symptoms and signs. A history of fever and cough are typical. Chills are common to all pneumonias although a single shaking chill has been classically associated with *Streptococcus pneumoniae*. An elevated temperature, rales, and tachypnea are common, but physical findings for consolidation are reported in less than 50 per cent of pneumonias.<sup>20, 85, 121</sup>

**Typical Pneumonia.** Typical pneumonia is a predominantly respiratory illness that evolves over 3 to 5 days in patients, with readily identifiable predisposing risk factors. The average age of patients is the same as that of the general inpatient hospital population. The cough is usually productive of purulent sputum. The etiologic agents are usually bacterial. The disease is usually acquired by aspiration of colonized mouth flora.

**Atypical Pneumonia.** Atypical pneumonia is a respiratory illness with prominent extrapulmonary involvement. Atypical pneumonias tend to affect younger individuals with fewer identifiable risk factors. They are often seasonal in nature or appear in epidemic outbreaks. Atypical pneumonia tends to evolve over 7 to 10 days, with prominent headaches, malaise, and myalgias associated with progression of the respiratory symptoms from the upper to the lower respiratory tract. The cough tends to be dry or mucoid. Atypical pneumonias are usually caused by nonbacterial agents. They evolve from a descending upper respiratory tract infection, and patients characteristically exhibit relative bradycardia for the observed temperature, the pulse rising less than 15 beats per minute per degrees C of fever.<sup>30, 79, 96, 104, 138</sup>

Although there is some overlap, each syndrome is sufficiently distinct to be treated as an independent diagnostic and therapeutic group. Within each category, individual etiologic agents remain difficult to differentiate and require more specific tests for identification.<sup>48</sup>

**Chest Roentgenogram.** The chest roentgenogram<sup>1</sup> is almost invariably abnormal. Three major patterns are associated with pneumonias acquired via the tracheobronchial tree. *Air space or lobar pneumonia* is characterized by a dense, well-demarcated lobar or segmental opacity with air-bronchograms. The radiologic density is caused by an infection that produces abundant alveolar edema with little cellular inflammation and moves easily through interalveolar connections. *Bronchopneumonia* is the most common pattern in community-acquired pneumonias and is characterized by patchy infiltrates associated with terminal airways.<sup>121</sup> Bronchopneumonias are usually inflammatory, and the spread of the infection among alveolar units is limited by a vigorous cellular response. Microabscess formation may be seen and healing may be associated with fibrosis. *Interstitial pneumonias* spare the alveolar spaces and produce finely nodular or reticulonodular densities. Pneumonias acquired via the inhalation or aspiration routes tend to be more common in the lower lobes. Pneumonias acquired via the hematogenous route tend to be patchy, nodular, and basilar or random in location. The patterns de-

pend more on the pathophysiology of the infection than the infecting organism and are generally unreliable indicators of the specific infectious etiology.<sup>1, 98, 153</sup> The presence of a lobar or segmental process, cavitation or abscess formation of a bulging fissure tends to correlate with a bacterial process. Fibronodular densities with cavitation in the apical and posterior segments of upper lobes is suggestive of a mycobacterial process. Pleural effusions are present in 20 to 25 per cent of pneumonias regardless of etiology, and volume loss without an underlying obstructing lesion may be seen in 20 to 45 per cent of pneumonias.<sup>72, 98</sup>

The prior existence of COPD or bullous disease may modify the appearance of a classic pneumonia, and dehydration may produce a time lag before an infiltrate develops on a chest film.

Resolution of the chest film characteristically lags behind improvement of the patient's clinical condition. Chest roentgenograms take a median of 6 weeks to resolve in bacterial pneumonias. Seventy-five per cent resolve by 14 weeks and 83 per cent by 22 weeks. Delayed resolution is seen in older, malnourished patients, smokers, and patients with COPD. Legionella infections have a particularly prolonged time course, whereas mycoplasma and viral infections resolve more quickly.<sup>1, 72, 98</sup>

### Therapeutic Approach

**Antibiotic Selection.** Pneumonia is typically an acute illness, and events that determine outcome often develop early in the course. Mortality may be influenced by the timing of antibiotic therapy. The earlier effective treatment is started, the better the outcome. Patients who receive prehospital antibiotic therapy may have a better survival than patients whose first treatment came on hospitalization.<sup>20, 97</sup> The choice of antibiotics begins with consideration of the major clinical syndrome and a knowledge of the organisms most likely to be involved. The physician must decide whether the gram stain is of sufficient quality to be reliable or whether the organisms suggested by the gram stain fit the patient's presentation. If the sputum provides diagnostic information, the antibiotic regimen can be specifically directed. If such information is lacking, antibiotics must be prescribed to cover the most likely possibilities given the clinical picture.<sup>36</sup>

The major cause of error in sputum sampling is contamination by oropharyngeal flora. A 1:1000 mixture of saliva with respiratory tract secretions can cause a 50 per cent contamination of the sputum specimen. Murray and Washington<sup>113</sup> showed that an adequate sputum sample may be identified by more than 25 neutrophils per low power (100 ×) field and fewer than ten squamous epithelial cells in the same field. With these criteria, a 90 per cent concordance between sputum gram stain and culture results can be expected, but as Van Scoy<sup>157</sup> observed, strict adherence to these criteria leads to a rejection of 75 per cent of all specimens submitted. Relaxation of these standards leads to a higher percentage of acceptable sputa but a lower diagnostic accuracy.<sup>10, 13, 19, 66, 86, 151</sup>

Table 2. Common Typical Bacterial Pneumonias

| ORGANISM              | STREPTOCOCCUS<br>PNEUMONIAE                                        | HAEMOPHILUS INFLUENZAE                                      | GRAM-NEGATIVE BACTERIA<br>KLEBSIELLA, E COLI,<br>PSEUDOMONAS                                                                                      |
|-----------------------|--------------------------------------------------------------------|-------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------|
| References            | 7,8,109,121,122,131                                                | 126, 127, 115, 16, 39,<br>88, 160                           | 74,87                                                                                                                                             |
| Prevalence*           | 61.3                                                               | 10.6                                                        | 8.8                                                                                                                                               |
| Gram stain            | Gram positive diplo-<br>coccus                                     | Gram-negative coccoba-<br>cillus                            | Gram-negative rods                                                                                                                                |
| Antibiotics           | Penicillin                                                         | Ampicillin/amoxicillin                                      | Ceph III, aminoglyco-<br>side                                                                                                                     |
| Unusual fea-<br>tures | Erythromycin Ceph I-<br>II single shaking<br>chill<br>20-60%, ALPS | TMβ, Ceph II, chloram-<br>phenicol<br>Beta-lactamase in 25% | Amox/clav, TM-S, chlor-<br>amphenicol<br>Nursing home patients,<br>ETOH abuse, Klebsi-<br>ella in upper lobes<br>COPD, CHF, mixed in-<br>fections |

\* Percent among bacterial pneumonias.

Abbreviations: Ceph I, cephalosporin, 1st generation; Amox, amoxicillin/clavulanate; TM-S, trimethoprim-sulfa; CHF, congestive heart failure; ALPS, alcoholism, leukopenia, pneumococcal sepsis; DFA, direct fluorescent antibody.

Tables 2 and 3 list the commonest forms of typical and atypical community-acquired pneumonias, their prevalence and clinical characteristics.

In the absence of adequate sputum or epidemiologic evidence, an empiric antibiotic regimen should be chosen that will cover the most likely pathogens.

For typical pneumonias, the normal host most likely will be infected with *Streptococcus pneumoniae*. Penicillin represents the ideal choice of therapy.<sup>130</sup> Patients with underlying lung diseases are most likely to have *Streptococcus pneumoniae* or *Hemophilus influenzae*. Ampicillin, amoxicillin, or a second-generation cephalosporin constitute adequate coverage. The nursing home patient with a sig-

Table 3. Common Atypical Pneumonias

| ORGANISM              | MYCOPLASMA PNEUMONIAE                                                                                | CHLAMYDIA (TWAR)                                              | VIRI                                         |
|-----------------------|------------------------------------------------------------------------------------------------------|---------------------------------------------------------------|----------------------------------------------|
| References            | 3,47,92,28,70,120                                                                                    | 59,80,96,102,104,101                                          | 58,96,138                                    |
| Prevalence*           | 41.6                                                                                                 | 8.8                                                           | 50.4                                         |
| Diagnosis by          | Cold agglutinins, CF<br>antibody                                                                     | Antibody titer                                                | Serology, cultures,<br>clinical presentation |
| Treatment             | Erythromycin, tetracy-<br>cline                                                                      | Tetracycline                                                  |                                              |
| Unusual fea-<br>tures | Bronchitis common,<br>prominent cough, ex-<br>trapulmonary dis-<br>ease, hemolytic ane-<br>mia, HBSS | Little extrapulmonary<br>involvement, bron-<br>chitis unusual |                                              |
| Age                   | School age (through<br>college)                                                                      | Peak age 30                                                   |                                              |

\* Percent among atypical pneumonias.

Abbreviation: HBSS, sickle cell anemia.

Table 2. (Continued)

| LEGIONELLA                                                                                                         | STAPHYLOCOCCUS<br>AUREUS                                                                                                                                         | ANAEROBES                                                                                             | BRANHAMELLA<br>CATARRHALLIS             |
|--------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|-----------------------------------------|
| 30,34,67,155,158<br>5.7                                                                                            | 83,114,116,161,167<br>6.4                                                                                                                                        | 11,12,14,90,110,163<br>4                                                                              | 95,101,144,148,164<br>0.3               |
| DFA, Dieterie stains<br>only                                                                                       | Gram-positive cocci<br>in clusters                                                                                                                               | Mixed flora                                                                                           | Gram-negative diplo-<br>coccus          |
| Erythromycin                                                                                                       | Methicillin                                                                                                                                                      | Penicillin, clindamy-<br>cin                                                                          | Tetracycline, amoxi-<br>cillin + clav   |
| Rifampin as 2nd drug                                                                                               | Vancomycin                                                                                                                                                       | Ceftizoxime                                                                                           | TM-S                                    |
| Epidemic, warm<br>months, pulse defi-<br>cit, systemic toxic-<br>ity, diagnosis by<br>IFA titer, hypona-<br>tremia | Associated with in-<br>fluenza epidemics<br>(aerogenous), IV<br>drug abuse (hema-<br>togenous) cavitat-<br>ing nodules, soft-<br>tissue focus in<br>hematogenous | Superior segments of<br>lower lobes, aspi-<br>ration history cavi-<br>tation and abscess<br>formation | COPD association,<br>beta-lactamase 75% |

nificant risk of gram-negative pneumonia may need a second-generation cephalosporin for adequate coverage.<sup>49</sup> Although gram-negative pneumonias have a higher prevalence among alcoholics, *Streptococcus pneumoniae* and *Hemophilus* are still the most common pathogens. With a history of aspiration, bacteroides should be covered by penicillin or clindamycin.<sup>90</sup> The intravenous drug abuser, the diabetic, or the patient with apparent staphylococcal skin lesions is best covered with an antistaphylococcal penicillin such as methicillin or nafcillin.<sup>36, 45, 51, 55, 94, 106, 130, 143, 162</sup>

*Legionella* infections appear sufficiently uncommon outside of epidemic settings to discourage routine empiric coverage.<sup>38, 141</sup> Erythromycin would be indicated if legionellosis were suspected.

Table 3. (Continued)

| INFLUENZA A AND B                                       | ADENOVIRUS                                                    | RESPIRATORY SYNCYTIAL<br>VIRUS                         | VARICELLA-ZOSTER<br>VIRUS                                           |
|---------------------------------------------------------|---------------------------------------------------------------|--------------------------------------------------------|---------------------------------------------------------------------|
| 138                                                     | 128,96,138                                                    | 138,159,169                                            | 138,44,68                                                           |
| Culture, antibody<br>titer                              | Culture, serology                                             | —                                                      | Clinical picture, rash<br>serology                                  |
| Prophylaxis, Amanta-<br>dine in 1st 48 hr<br>for A only | None                                                          | Ribavirin                                              | Acyclovir<br>Ara-A                                                  |
| Bacterial superinfec-<br>tion                           | Postviral broncho-<br>spasm, closed pop-<br>ulation epidemics | Bronchiolitis in chil-<br>dren, pneumonia<br>in adults | Millary chest x-ray,<br>pleural effusion,<br>immune compro-<br>mise |
| Any                                                     | Young adult                                                   | Young children                                         | Any                                                                 |

For atypical pneumonias, the most likely treatable organism will be *Mycoplasma pneumoniae*, best managed with erythromycin. Because of its relatively broad spectrum, erythromycin is a good antibiotic choice for situations where the clinician cannot distinguish typical from atypical pneumonia.<sup>30</sup>

Most pneumonias will show a response to adequate antibiotic therapy within 72 hours. Failure to respond is often related to the patient's underlying condition, but an inaccurate initial assessment, a mixed infection that is inadequately covered, a complication such as empyema, drug fever, or a new superimposed process should be considered. Available bacteriologic and serologic information should be reviewed and the antibiotic regimen revised as needed.<sup>42</sup>

For hospitalized patients, intravenous antibiotics should be given at least until the temperature decreases. Oral antibiotics may then be substituted. Total duration of therapy ranges from 10 days to 3 weeks depending on the severity of the infection and the organism involved.

**Supportive Care.** The most serious danger in pneumonia is hypoxemia. Supplemental oxygen sufficient to maintain an oxygen saturation above 90 per cent must be provided by mask, nasal prongs, or by intubation and positive pressure ventilation if necessary. Adequate hydration and nutrition must be assured. Airway suctioning and postural drainage may help those patients unable to clear their own secretions. The physician should be vigilant for late complications such as empyema, sepsis, and multiple organ failure. Although the mortality rate for pneumonia has declined since the beginning of the antibiotic era, it remains at about 10 to 15 per cent, and is even higher with certain infectious organisms and risk groups.<sup>130, 154, 166</sup>

## Tuberculosis

Tuberculosis<sup>53</sup> is a pulmonary infection due to mycobacterium tuberculosis. Nontuberculous mycobacteria can cause similar clinical illnesses. Infection is usually acquired by inhalation of aerosolized mycobacteria coughed by an individual with active pulmonary tuberculosis. Infection is accompanied by the acquisition of delayed hypersensitivity to intradermal tuberculin skin testing, the purified protein derivative (PPD) Mantoux test. Infection may be self-limited or manifest as primary disease with hilar or mediastinal adenopathy, lower lobe pulmonary infiltrates, hematogenous or miliary tuberculosis, or a lymphocytic pleural effusion. Self-limited infections may reactivate with a decrease in immunocompetence and present as miliary tuberculosis or as the reactivation form of pulmonary tuberculosis with apical fibronodular infiltrates.<sup>53, 149</sup>

Tuberculosis is a disease associated with poverty, overcrowding, ethanol abuse, diabetes, malnutrition, end-stage renal disease, malignancy, HIV infection, and immunosuppressive therapy. Two thirds of tuberculosis patients are men with an average age of 40 to 50 years.<sup>53, 76</sup>

**Diagnosis.** Tuberculosis is often misdiagnosed at the time of hospital admission, usually because it has not been considered or has

been confused with lung cancer, bronchitis, bacterial pneumonia, congestive heart failure, or sarcoidosis. Delay in diagnosis is more likely in the elderly.<sup>46, 71, 75, 100</sup>

**Signs and Symptoms.** Pulmonary tuberculosis presents as a chronic disease with an average duration of symptoms of 6 weeks. Cough, malaise, sweats, and weight loss are present in the majority of cases. Fever, fatigue, anorexia, hemoptysis, dyspnea, and pleuritic chest pain are seen in 20 to 40 per cent of cases. Fifteen to 20 per cent of tuberculosis patients may be asymptomatic. One third of tuberculosis patients have a prior history of tuberculous infection. The physical examination is nonspecific. Fever above 100 degrees F, wasting, rales, and consolidation are all present in 25 to 40 per cent of cases. Hepatomegaly is seen in 20 per cent.<sup>76, 77, 100</sup>

**Chest Film.** The chest roentgenogram is more likely to be helpful in making an accurate diagnosis of pulmonary tuberculosis than is the history or physical examination.<sup>40</sup> Reactivation tuberculosis classically presents as a fibronodular density in apical and posterior segments of the upper lobes and superior segments of the lower lobes. Cavities are usually small and multiple. Primary tuberculosis is characterized by hilar or mediastinal adenopathy, usually unilateral, a pleural effusion, or lower lobe infiltrates.<sup>124</sup> Khan et al<sup>77</sup> called attention to a 35 to 50 per cent incidence of primary tuberculosis patterns among the elderly. Although the majority of pulmonary tuberculosis patients today still present with a classic apical reactivation pattern,<sup>40, 124</sup> tuberculosis infection in patients with AIDS often presents with the primary pattern.<sup>132</sup>

**Bacteriology.** A definitive diagnosis of pulmonary tuberculosis is made by demonstration of acid-fast bacilli in the sputum. Gastric aspirates may yield acid-fast bacilli as well, but are not independently positive. Smear positive patients are by definition infectious. Positive smears will be seen in 50 to 85 per cent of pulmonary tuberculosis patients.<sup>60, 100</sup> If a tuberculosis suspect is smear negative, attempts should be made to induce sputum with inhaled heated saline mist. If still negative, bronchoscopy may be considered in an attempt to collect sputum samples. If bronchoscopic washings do not reveal acid-fast bacilli, the patient should be followed clinically pending final culture results. If the PPD is positive, the patient should be treated while awaiting cultures.

**Purified Protein Derivative.** A skin test with 5 tuberculin units PPD is positive in 48 to 88 per cent of patients with active tuberculosis with a mean induration of 17.4 mm.<sup>76, 77, 100</sup> The most common reasons for a lack of skin test positivity is anergy or failure to perform the test. The probability of active tuberculosis in the presence of a negative PPD without anergy is about 10 per cent.<sup>107</sup>

**Therapy.** The cornerstone of antituberculous therapy<sup>15</sup> is the use of multiple drugs for a sufficient duration and the promotion of compliance with therapy.

Patients infected with mycobacterium tuberculosis without evidence of active disease should be treated with isoniazid (INH) for 6

to 9 months. Because of the competing risk of INH hepatitis, INH prophylaxis should be restricted to patients whose risk of active tuberculosis exceeds that of INH hepatitis.

Standard chemotherapy for most pulmonary and extrapulmonary tuberculosis consists of daily isoniazid 300 mg per day, rifampin 600 mg per day, and pyrazinamide 15 to 30 mg per kg per day for 2 months followed by 4 months of isoniazid and rifampin for a total course of 6 months. Alternatively, INH and rifampin may be used without the addition of pyrazinamide for a total of 9 months. The shorter course is encouraged because of the improved likelihood of compliance. Ethambutol 15 to 25 mg per kg per day can be added to all regimens in the presence of suspected INH resistance. Patients on INH should be watched for possible drug-related hepatitis. Patients on ethambutol should be followed for possible optic neuritis. Treatment failures occur in about 4 per cent. For relapses, INH and rifampin are continued with the addition of two new antituberculous agents not previously used. Duration of therapy should be extended to 12 to 18 months.

Ethambutol should not be used in children. In pregnancy, standard therapy is safe with the exception of pyrazinamide, whose safety has not been established. Pyridoxine supplementation should be given routinely to avoid neuropathy. Postpartum breast feeding is safe. Although active cases should be treated, prophylaxis for tuberculous infections should be delayed until the end of the pregnancy.

The median time for defervescence following institution of antituberculosis chemotherapy is 10 to 16 days. Eighty-eight per cent of patients are afebrile by 6 weeks and all by 16 weeks. Patients with advanced disease and cavitation are more likely to have a prolonged febrile course. Bacterial superinfection is unusual as a cause of prolonged fever but may be suspected in the event of a secondary rise in temperature after resolution of the fever.<sup>27, 78</sup>

## SUMMARY

Community-acquired respiratory tract infections are common causes of morbidity that require prompt and effective management. Upper respiratory tract infections should be evaluated for their potential for airway compromise and likelihood of a bacterial etiology. Acute lower respiratory tract infections often must be treated on empiric grounds. The presenting clinical pattern may give useful clues as to the best antibiotic therapy. High-risk patients must be hospitalized and may require intensive care, whereas lower risk patients may be managed on an outpatient basis. Chronic or subacute lower respiratory tract illness should be approached with tuberculosis in mind.

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## Viral Hepatitis

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Intensive research by many investigators from around the world has advanced the understanding of the epidemiology, clinical course, treatment, and prevention of viral hepatitis. The viruses responsible for several types of hepatitis have been identified and extensively studied. This knowledge has impacted on the practice of anesthesiology both in terms of patient care as well as the occupational health of anesthesia personnel.

Although many viruses (for example, cytomegalovirus and Epstein-Barr virus) may produce hepatitis, this review covers only hepatitis produced by four hepatotropic viruses: type A (infectious) hepatitis; type B (serum) hepatitis; non-A, non-B hepatitis; and delta hepatitis (Table 1). Annual incidence rates of the number of reported cases of viral hepatitis in the United States are published by the Centers for Disease Control (CDC).<sup>17</sup> Although it is recognized that the rate of documented cases underestimates the actual number,<sup>1</sup> certain trends are evident (Fig. 1). In the United States, the incidence of hepatitis B has steadily increased since the early 1980s to the current estimate of over 300,000 cases per year. Over 200 million people worldwide are infected with the hepatitis B virus and it has become the greatest single cause of primary liver cancer. Because of the constantly enlarging pool of chronic carriers of hepatitis B virus, the high infectivity of blood from carriers, and the frequency of blood exposure, this form of hepatitis is the major infectious occupational hazard for physicians. Concurrently, there has been a decrease in the incidence of hepatitis A, and non-A, non-B hepatitis has become the most frequent cause of post-transfusion hepatitis. Although anesthesiologists do not usually assume responsibility for the primary care of patients with infectious hepatitis, they should have an understanding of the epidemiology, including the mode of transmission of the diseases, the available methods for identifying infected patients, and the strategies recommended to prevent occupationally acquired infections.

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Table 1. *Viral Hepatitis: Comparison of Agents and Clinical Diseases*

| CHARACTERISTIC                           | HEPATITIS A            | HEPATITIS B                     | NON-A, NON-B HEPATITIS            | DELTA HEPATITIS                         |
|------------------------------------------|------------------------|---------------------------------|-----------------------------------|-----------------------------------------|
| Virus                                    | 27-nm RNA picornavirus | 42-nm DNA Hepadna virus         | Unknown                           | 35-nm defective RNA virus               |
| Incubation period (days)                 | 15-45                  | 40-180                          | 15-150                            | 28-150                                  |
| Epidemiology                             | Fecal-oral             | Parenteral, venereal, perinatal | Parenteral, fecal-oral, perinatal | Parenteral                              |
| Transfusion-related*                     | Rare                   | 5-10%                           | 90-95%                            | ?                                       |
| Chronic hepatitis                        | No                     | 5-10%                           | 5-50%                             | Coinfection <5%, superinfection >75%    |
| Carrier state                            | No                     | Adult 5-10%, infant 70-90%      | >50%                              | Coinfection <5%, superinfection >75%    |
| Fulminant hepatic failure                | Rare                   | 1%                              | <5%                               | Coinfection 1-10%, superinfection 5-20% |
| Associated with hepatocellular carcinoma | No                     | Yes                             | ?                                 | ?                                       |

\* Values are for per cent of cases of transfusion-related hepatitis caused by each type of virus.

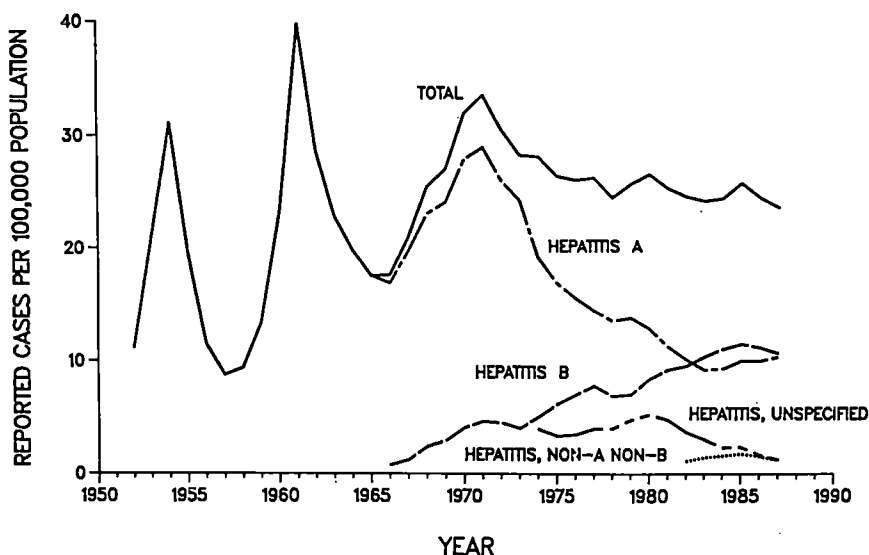


Figure 1. Cases of hepatitis in the United States, from 1952 to 1987, reported to the Centers for Disease Control. (From Centers for Disease Control Summary of notifiable diseases, United States, 1987. MMWR 36:54, 1987.)

## TYPE A HEPATITIS

Hepatitis A, formerly called infectious hepatitis, is caused by the hepatitis A virus (HAV), a 27-nm RNA agent that is a member of the picornavirus family (see Table 1). HAV is usually spread from person to person by the fecal-oral route as a result of overcrowded conditions or poor hygiene. Transmission is usually through close personal contact but epidemics from contaminated food or water also occur. HAV has occasionally been transmitted by blood transfusion. About 40 per cent of all cases of hepatitis reported in the United States are hepatitis A.<sup>17</sup>

### Clinical Course

Clinical symptoms of hepatitis A such as anorexia, nausea, fever, malaise, and jaundice begin about 28 (range 15 to 45) days after infection. Hepatitis A is usually a self-limited illness, and in fact, most HAV infections in children are asymptomatic. Hepatitis A does not produce chronic hepatic disease or cirrhosis, and mortality from the disease is about 0.6 per cent.

### Transmission of Hepatitis A Virus

Typically, HAV is present in high concentration in the stools of infected patients only until the onset of clinical symptoms when the numbers rapidly decline. Therefore, the greatest risk of transmission

of hepatitis A occurs during the asymptomatic period. Because there is not a chronic form or carrier state of HAV infection and because most patients with hepatitis A are not hospitalized, anesthesia personnel have only a small risk of contracting the infection during their care of patients.

When severe symptoms require that patients be hospitalized, they are usually not infectious because they are likely to have already entered the phase when they are no longer shedding large numbers of HAV in the stool. Occasionally, the virus may be found in feces for a longer duration, and hence it is recommended that patients with hepatitis A be treated as potentially infectious for 2 weeks after the onset of jaundice. Hospitalized patients suspected of having hepatitis A should be placed in isolation using enteric precautions.<sup>30</sup> There have been outbreaks of hepatitis A in hospital staff resulting from undiagnosed infected patients who have fecal incontinence. Most of these outbreaks have involved infants in intensive care unit settings where there have been high rates of transmission to staff. Standard precautions regarding the handling of feces and body fluids are adequate for preventing transmission of HAV to health care workers.

### Serologic Diagnosis

Although HAV is not detectable in the serum, the first marker of infection after the incubation period is the presence of the virus in the stool (Fig. 2). Fecal shedding of HAV occurs for about 1 to 2 weeks prior to the onset of symptoms and then declines rapidly. At the time

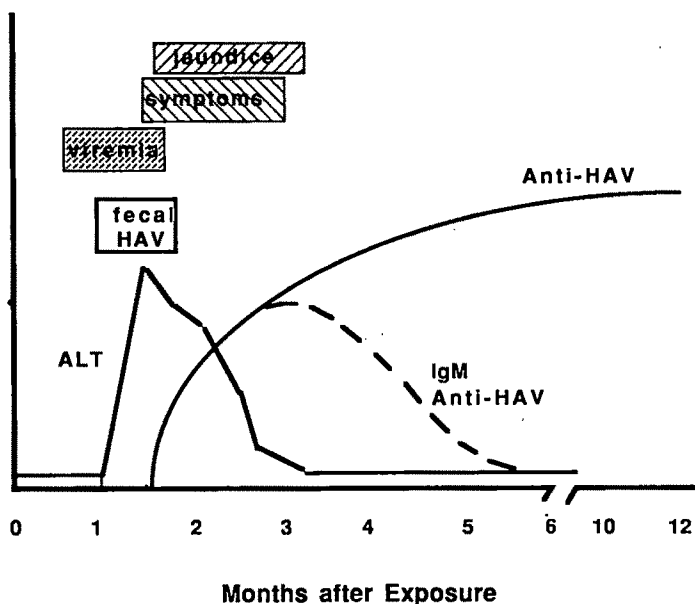


Figure 2. Typical course of a patient with HAV infection.

**Table 2.** *Antigens and Antibodies in Viral Hepatitis*


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|                                                                                                                                         |                                                                                                                                                                                                            |
|-----------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Hepatitis A Virus</b>                                                                                                                |                                                                                                                                                                                                            |
| Antibodies                                                                                                                              |                                                                                                                                                                                                            |
| Anti-HAV total:                                                                                                                         | Total antibodies (IgG and IgM) to HAV; indicates recent acute as well as past infection                                                                                                                    |
| IgM anti-HAV:                                                                                                                           | IgM antibody to HAV; this antibody is present only during the acute phase (4 to 6 months) of infection                                                                                                     |
| <b>Hepatitis B Virus (HBV)</b>                                                                                                          |                                                                                                                                                                                                            |
| Antigen                                                                                                                                 |                                                                                                                                                                                                            |
| HBsAg:                                                                                                                                  | Hepatitis B surface antigen: outer surface component of virus. Indicates either acute or chronic infection                                                                                                 |
| HBcAg:                                                                                                                                  | Hepatitis B core antigen: antigen found in the core of HBV. It is detectable only in infected hepatic tissue and cannot be found in serum                                                                  |
| HBeAg:                                                                                                                                  | Hepatitis B e antigen: Soluble protein associated with HBV core. Presence correlates with high levels of infectivity                                                                                       |
| Antibodies                                                                                                                              |                                                                                                                                                                                                            |
| Anti-HBs:                                                                                                                               | Antibody to HBsAg; indicates clinical recovery from infection and provides lasting immunity. It is the antibody produced in response to the HBV vaccine and may be present as a passive antibody from HBIG |
| Anti-HBc:                                                                                                                               | Total antibody (IgM and IgG) to HBcAg; may indicate active acute or chronic infection or past infection                                                                                                    |
| IgM anti-HBc:                                                                                                                           | IgM antibody to HBcAg; indicates acute HBV infection and is rarely present in chronic infection                                                                                                            |
| Anti-HBe:                                                                                                                               | Antibody to HBeAg; during acute infection, its presence indicates resolution of infection; when present in serum of HBsAg carrier, suggests lower titer of HBV                                             |
| <b>Non-A, non-B hepatitis</b>                                                                                                           |                                                                                                                                                                                                            |
| Candidate antigen and antibodies have recently been identified; currently, clinical diagnosis is by exclusion                           |                                                                                                                                                                                                            |
| <b>Epidemic non-A, non-B hepatitis</b>                                                                                                  |                                                                                                                                                                                                            |
| Responsible candidate virus has been identified; causes large epidemics in Asia and North Africa; fecal-oral or waterborne transmission |                                                                                                                                                                                                            |
| <b>Delta Hepatitis Virus</b>                                                                                                            |                                                                                                                                                                                                            |
| Antigen                                                                                                                                 |                                                                                                                                                                                                            |
| HD Ag:                                                                                                                                  | Hepatitis D antigen: antigen associated with HDV; found in liver tissue                                                                                                                                    |
| Antibodies                                                                                                                              |                                                                                                                                                                                                            |
| Anti-HD:                                                                                                                                | Total antibody (IgM and IgG) to HDAg; indicative of past or present HDV infection                                                                                                                          |
| Anti-HD IgM:                                                                                                                            | IgM antibody to HDAg; indicates continued HDV inflammatory liver disease                                                                                                                                   |

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that the patient becomes symptomatic or jaundiced, antibody to HAV (anti-HAV) is usually detectable in the serum (Table 2). Initially, the anti-HAV primarily consists of the IgM subgroup. Within 3 to 6 months, the IgM anti-HAV becomes undetectable while IgG anti-HAV titer peaks and remains present for many years. Thus, IgM anti-HAV can be used to diagnose acute hepatitis A whereas total or IgG anti-HAV should be used as a marker of previous HAV infection (see Fig. 2).

### **Immune Globulin for Prophylaxis of Hepatitis A**

Immune globulin (IG) is prepared from human plasma and contains antibodies against HAV and the hepatitis B virus. Commercially

prepared IG has been shown not to transmit hepatitis or the human immunodeficiency virus (HIV), the virus responsible for AIDS.<sup>15</sup> When given prior to exposure or during the early incubation period of hepatitis A, IG is 80 to 90 per cent effective in protecting against the clinical illness.<sup>55</sup>

The CDC recommends the use of IG for preexposure prophylaxis for travelers who will be going to developing countries, especially where they may be eating or living in areas with poor sanitary conditions.<sup>41</sup> Administration of IG is also recommended for individuals who have had close personal contact with persons with serologically confirmed hepatitis A.<sup>41</sup> Although routine IG prophylaxis of health care workers is not indicated, it may be used in staff who have been exposed to feces of infected patients under certain conditions. Under these circumstances, IG should be administered intramuscularly as soon as possible after a documented exposure. Administering IG more than 2 weeks post-exposure is not indicated since its efficacy declines and is very low after this duration.

### Hepatitis A Vaccine

Several approaches for formulating a hepatitis A vaccine are currently being investigated.<sup>59</sup> Vaccines have been prepared from killed HAV that was recovered from the liver of infected animals, and these have produced immunologic protection against repeat HAV infection when administered to animals.<sup>60</sup> Vaccines against hepatitis A using both inactivated and live attenuated virus have been developed to provide active immunization in groups who are at high risk of HAV infection. These vaccines are currently undergoing early clinical trials in humans.

## TYPE B HEPATITIS

Research during the past quarter century has unraveled many of the mysteries that had existed about viral hepatitis, and the events surrounding the acquisition of this knowledge provide an example of the successful use of modern scientific technology. Although it had been shown before World War II that transfusion of whole blood, plasma, or blood products could transmit hepatitis, one of the largest epidemics of viral hepatitis occurred in 1942 when approximately 50,000 U.S. Army personnel developed icteric hepatitis after receiving specific lots of yellow-fever vaccine.<sup>28</sup> Recently, through serologic testing, it was demonstrated that hepatitis B virus had contaminated the human serum used to stabilize the vaccine.<sup>67</sup>

Krugman and coworkers<sup>47</sup> achieved a major advancement in the understanding of viral hepatitis when they clearly identified and characterized the epidemiologic and clinical distinctions between two types of hepatitis ("infectious" and "serum") in patients at the Willowbrook State School. Using serum transaminase activity as a marker of liver disease, these investigators were able to determine that there

diseases based on differences in incubation period and duration about the same time, the fortuitous discovery of a new antigen that was found with high frequency in the serum of patients with leukemia provided a useful marker for identifying "serum" hepatitis.<sup>8</sup> Subsequent observations demonstrated that the "Australia antigen," which Blumberg had discovered in leukemic patients, was actually linked with hepatitis B and was present in the Willowbrook patients who had the form of hepatitis characterized by a long incubation period.<sup>9, 34</sup>

These events provided momentum to the ongoing research in the area of hepatitis B. In a relatively brief period using the technology of DNA hybridization and recombinant techniques, the hepatitis B virus has been characterized,<sup>62</sup> much of its genome identified, and vaccines for prevention of the disease in humans were created and put into clinical practice. The intensive study of the epidemiology and virology of hepatitis B has provided information that is being used toward the worldwide control of the disease. The modes of transmission of hepatitis B in the workplace to anesthesia personnel and other health care workers have been delineated, and strategies have been suggested for preventing occupational transmission of the disease.

### Hepatitis B Virus

The hepatitis B virus (HBV) is part of the family of animal viruses designated hepadna viridae, a group of viruses that are hepatotropic and can produce persistent chronic infection (see Table 1). The complete hepatitis B virion can be identified in the serum of patients while there is active viral multiplication in the liver. The 42-nm virion consists of an envelope that carries the hepatitis B surface antigen (HBsAg), a nucleocapsid (hepatitis B core antigen, HBcAg) containing a circular molecule of partially double-stranded DNA, a DNA polymerase, a protein kinase, and a DNA-linked protein<sup>77</sup> (see Table 2). Hepatitis B "e" antigen (HBeAg), which can be identified in the serum during active HBV infection, is derived from HBcAg that has undergone a conformational change.<sup>54</sup> During active infection, rod-like and 22-nm spherical particles consisting of HBsAg are also present and represent empty viral envelopes.

### Hepatitis B Virus Infection and Serologic Markers

There are several possible outcomes after infection with HBV: acute, symptomatic hepatitis; fulminant hepatitis; subclinical, asymptomatic disease; or development of the chronic carrier state. Approximately 90 per cent of adults will have a self-limited course after HBV infection with the majority being asymptomatic, 5 to 10 per cent of adults will go on to a chronic carrier state, and 1 per cent will have a fulminant form of hepatitis with a mortality rate greater than 50 per cent. The factors that determine the clinical course and outcome after HBV infection are not completely understood, but four have been identified that are associated with a higher carrier rate: (1) an immunodeficiency state either natural or secondary to other infections

or medication; (2) age at the time of HBV infection; (3) male predominance; and (4) genetic or racial factors. The most important of these is age; perinatal HBV infection results in a chronic carrier state in about 70 to 90 per cent of infected children whereas acute infection in adults results in 5 to 10 per cent remaining chronic carriers. Thus, patient factors such as cellular immunity rather than viral characteristics seem to be more important in determining outcome after HBV infection.

With the initial acute infection, the incubation time averages 75 days (range 40 to 180) and is directly related to the mode of exposure (percutaneous transmission shortest) and inversely to the infecting dose of HBV. HBsAg is the first marker of HBV detectable in the serum after infection (Fig. 3). Its titer usually peaks as the liver enzymes (aminotransferases) begin to increase and as the patient develops symptoms. Resolution of the acute infection usually occurs within 4 to 6 months. HBsAg generally declines at about the time of clinical recovery and improvement of aminotransferase levels. HBeAg appears in the serum shortly after HBsAg and is a marker that is used to monitor the infectivity and course of the patient. Seroconversion from HBeAg to anti-HBe suggests that the infection is resolving and is an event that usually occurs at the peak of clinical symptoms.

HBcAg can be detected only in hepatocytes but the antibody to HBcAg (anti-HBc) is present in serum shortly after HBsAg but before the onset of symptoms. Anti-HBc can be used as a marker for acute or past disease since the antibody is found in the serum for many years (usually for life) after the resolution of HBV infection. Initially, anti-HBc is totally composed of IgM antibody but after 6 to 18 months only IgG anti-HBc is detectable. Anti-HBc IgM can be used to separate recent from remote HBV infection.

Antibody to HBsAg (anti-HBs) is a serologic marker of recovery from infection and is the antibody that provides immunity against later HBV infections. Usually a window of time exists between the loss of HBsAg and the appearance of anti-HBs. If a patient is first seen during this period, only anti-HBc may be detectable as a marker of recent hepatitis B. Anti-HBs is present for years and along with anti-HBc can be useful to determine previously resolved infection. In some individuals, titers of one or both antibodies may decline so that they are undetectable.

After HBV infection, about a third of adults develop the classic clinical progression of symptoms associated with acute hepatitis B, a third have only a flu-like illness without jaundice, and a third are totally asymptomatic. The typical serologic course is characterized by a brief period during which HBsAg and HBeAg are present in the serum followed by the appearance of anti-HBs and anti-HBc. Patients usually do not have prolonged or significant aminotransferase elevations and may not come to medical attention at the time of the acute process. Past HBV infection may first be diagnosed when serologic screening turns up a positive test for either anti-HBs or anti-HBc.

About 1 per cent of patients with acute hepatitis B develop ful-

## ACUTE HEPATITIS B

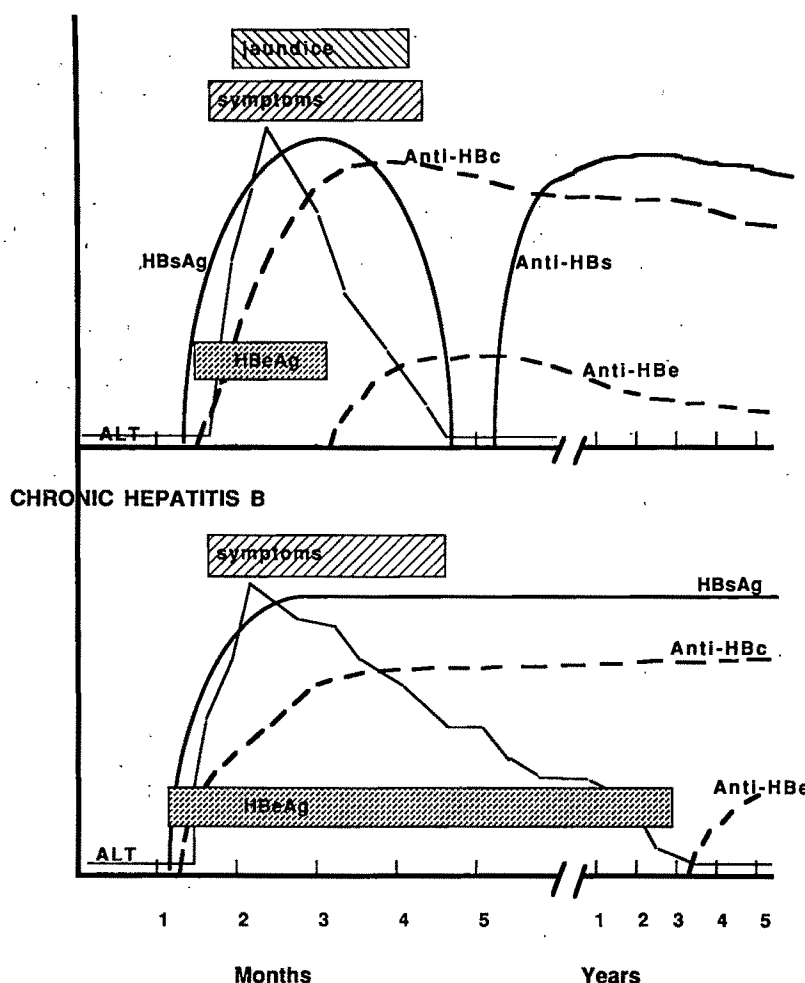


Figure 3. The typical clinical, biochemical, and serologic courses in acute (*upper*) and chronic (*lower*) hepatitis B.

minant hepatitis. Encephalopathy may be the first clinical sign of this form of the disease; other findings include high fever, reduction in liver size, asterixis, high levels of serum bilirubin, and prolonged prothrombin time. Serum aminotransferase levels may be very high initially but decline as hepatocytes are destroyed. In spite of the advances made in the care of patients with hepatic disease, the mortality rate with fulminant hepatitis B remains around 80 per cent.

A chronic carrier state, the persistence of HBsAg for longer than 6 months, occurs in approximately 10 per cent of infected adults (see

Fig. 3). HBeAg and anti-HBc remain detectable in the serum as in the initial stage of acute infection, but anti-HBs is never present. Patients who become chronic HBsAg carriers usually have an asymptomatic or mild clinical course with the acute infection, but may have significant elevation of serum aminotransferase levels. Carriers may or may not be symptomatic and may have a spectrum of biochemical or histologic evidence of liver involvement ranging from normal to chronic hepatitis.

Chronic hepatitis B has at least two morphologic variants: chronic persistent hepatitis and chronic active hepatitis. Chronic persistent hepatitis is typically characterized by normal hepatocytes, little hepatic fibrosis, and inflammation localized mainly to the portal tracts. The primary lesion in chronic active hepatitis is piecemeal necrosis whereas bridging hepatic and multilobular necrosis are present in more severe forms. With chronic active hepatitis there is continued progressive hepatocyte destruction leading to cirrhosis with portal hypertension and liver failure. There are no reliable serologic or clinical tests to predict which patients will become carriers or will develop chronic hepatitis.

### **Hepatitis B Virus Transmission**

The factors necessary for the successful transmission of HBV have been well defined.<sup>31</sup> The outcome after HBV transfer is related to the viral concentration in the source material, the volume of infectious material transferred, changes in viral infectivity occurring during transfer, and the method for introducing the virus into the recipient. HBV is usually present in high concentration in the blood of infected persons and thus, blood is a very efficient vehicle for HBV transmission and is the most important source of HBV in the health care setting. HBV is a hardy virus that can survive for prolonged periods in blood on environmental surfaces. In a laboratory setting, it was demonstrated that HBV that had remained in dried blood for 1 week was capable of producing clinical hepatitis B after inoculation into a chimpanzee.<sup>10</sup>

HBsAg is used as a marker of HBV and has been isolated from many body fluids including semen, vaginal secretions, synovial fluid, amniotic fluid, and peritoneal fluid. It is unusual for anesthesia personnel to have direct contact with these fluids. Other health care workers routinely wear gloves when obtaining or handling samples of these fluids so that they do not represent major risks in the occupational setting.<sup>20</sup> In many patients who carry HBV, HBsAg can be detected in saliva.<sup>78</sup> The HBV does not originate in the salivary gland but is found in the serum-derived fluid that is present around the roots of teeth. HBV-infected saliva inoculated subcutaneously into test animals was capable of transmitting infection but oral administration did not produce disease.<sup>66</sup> Epidemiologic surveys have not implicated nasal secretions, sputum, sweat, tears, and urine in the transmission of HBV in health care settings.

HBV may be spread by means of infected blood and body fluids, during homosexual or heterosexual intercourse, or from mother to in-

**Table 3. Prevalence of Hepatitis B Serologic Markers in Various Populations\***

| POPULATION GROUP                                        | PREVALENCE OF SEROLOGIC MARKERS OF HBV INFECTION |                 |
|---------------------------------------------------------|--------------------------------------------------|-----------------|
|                                                         | HBsAg (%)                                        | All Markers (%) |
| <b>High risk</b>                                        |                                                  |                 |
| Immigrants from areas of high HBV endemicity            | 13                                               | 70-85           |
| Clients in institutions for the mentally retarded       | 10-20                                            | 35-80           |
| Users of illicit parenteral drugs                       | 7                                                | 60-80           |
| Homosexually active men                                 | 6                                                | 35-80           |
| Household contacts of HBV carriers                      | 3-6                                              | 30-60           |
| Patients of hemodialysis units                          | 3-10                                             | 20-80           |
| <b>Intermediate risk</b>                                |                                                  |                 |
| Health-care workers with frequent blood contact         | 1-2                                              | 15-30           |
| Prisoners (male)                                        | 1-8                                              | 10-80           |
| Staff of institutions for the mentally retarded         | 1                                                | 10-25           |
| <b>Low risk</b>                                         |                                                  |                 |
| Health-care workers with no or infrequent blood contact | 0.3                                              | 3-10            |
| Healthy adults (first time volunteer blood donors)      | 0.3                                              | 3-5             |

\* Immunization Practices Advisory Committee: Recommendations for protection against viral hepatitis. MMWR 34:313, 1985.

fant in the perinatal period. Transmission occurs through parenteral routes such as transfusion of blood or blood products, use of contaminated needles or syringes, or accidental sticks with contaminated needles or sharp instruments. HBV probably does not cross intact skin or mucous membranes, but infection may occur through minute breaks in these barriers as may be found with dermatitis.

The CDC has used data obtained from screening projects to categorize the prevalence of current or previous HBV infection in various population groups (Table 3).<sup>41</sup> HBV infection is uncommon in healthy adults living in the United States (prevalence of 3 to 5 per cent from data from volunteer blood donors). This is in marked contrast to a 70 to 85 per cent prevalence and 15 per cent carrier rate in many Asian, Pacific Island, or sub-Saharan African inhabitants. The CDC data indicates that the incidence of hepatitis B in the United States has remained relatively constant over the past 5 years, but there has been an increase in the proportion of new cases with a history of intravenous drug use and a decline among homosexual males.<sup>14</sup> This probably reflects a decrease in high-risk sexual behavior in homosexual males in response to their concerns about HIV infection.

### **Hepatitis B in Anesthesia Personnel**

Because of their frequent contact with blood and body fluids, anesthesia personnel are included in the group of health care workers identified as having an increased risk of occupationally acquired hep-

**Table 4.** *Prevalence of Hepatitis B Seropositivity in Anesthesia Personnel*

| REFERENCE                       | STUDY POPULATION                                                  | PREVALENCE (%) |
|---------------------------------|-------------------------------------------------------------------|----------------|
| Denes et al <sup>24</sup>       | MDs at AMA meeting                                                | 17             |
| Berry et al <sup>5</sup>        | MDs and non-MD anesthetists in one U.S. department                | 23             |
| Berry et al <sup>7</sup>        | MDs and non-MD anesthetists in four U.S. departments              | 19             |
| Berry et al <sup>6</sup>        | Residents in seven U.S. departments                               | 13             |
| Fyman et al <sup>33</sup>       | NY inner-city hospital                                            | 49             |
| Malm et al <sup>52</sup>        | Anesthetists in teaching hospitals in Vancouver, Canada           | 12             |
| Chernesky et al <sup>21</sup>   | Anesthetists in Ontario, Canada                                   | 17             |
| Siebkke and Degre <sup>70</sup> | MD and non-MD anesthesia personnel in Norway                      | 4              |
| Carstens et al <sup>13</sup>    | South African anesthetists                                        | 18             |
| Sinclair et al <sup>71</sup>    | Anesthetists in Oxford, UK                                        | 3              |
| Janzen et al <sup>42</sup>      | Anesthesia personnel at Medical School of Hannover (West Germany) | 31             |

From Berry AJ, Katz JA: Hazards of working in the operating room. In Barash PG, Cullen BF, Stoelting RK (eds): *Clinical Anesthesia*. Philadelphia, Lippincott, 1989, p 80; with permission.

atitis B. Multiple surveys (Table 4) have documented that anesthesiologists have an increased prevalence of hepatitis B markers compared with the general population in the United States (3 to 5 per cent in healthy blood donors). One of the highest prevalences was reported from a large hospital in New York City where 49 per cent of the anesthesia personnel had serologic evidence of HBV infection.<sup>33</sup> In a large, multicenter study of four university-affiliated anesthesia departments, 19 per cent of physician and non-physician members of the anesthesia care team were seropositive.<sup>7</sup> This survey showed that HBV was the most frequent etiology when anesthesia personnel developed symptomatic hepatitis after entering the specialty. HBV seropositivity was documented in some anesthesia personnel who had no clinical history of hepatitis and must have had asymptomatic hepatitis B. The data from the U.S. multicenter study by Berry et al<sup>7</sup> indicated that 59 per cent of all seropositive individuals denied a prior history of hepatitis B and is consistent with the 50 per cent rate of asymptomatic HBV infection reported in other groups.<sup>38</sup>

The increased risk of HBV infection is not limited to anesthesiologists in practice but begins during the training period. Berry et al<sup>6</sup> found that at seven universities, 13 per cent of residents who began anesthesia training programs directly after medical school had serologic markers of hepatitis B, and those who had other residencies or medical experience prior to anesthesia had an even higher seroprevalence.

It is noteworthy that anesthesia personnel who used information in the hospital chart in an attempt to identify HBV carriers had a

seroprevalence of HBV markers, which was similar to those who did not.<sup>7</sup> This suggests that use of the medical history is not an effective strategy to prevent occupational transmission of HBV from patients. A survey of hospitalized patients has demonstrated that although 1.5 per cent were HBsAg seropositive, the majority did not have clinical hepatitis and were not identified as HBV carriers in their medical records.<sup>51</sup> The medical history, physical examination, and routinely ordered preoperative laboratory tests are generally not adequate to diagnose unrecognized HBV carriers, and serologic tests for HBV infection are not routinely performed prior to surgery. Therefore, in most instances, anesthesia personnel are unable to identify patients capable of transmitting HBV.

### **Prevention of Hepatitis B Virus Infection**

Strategies to prevent occupational transmission of HBV must be consistent with the known epidemiology of the disease and be acceptable modifications of the work practices of anesthesia personnel. Currently these strategies include the use of passive and active immunization and "universal precautions," a set of recommendations to prevent transmission of blood-borne infections in the health-care setting.

### **Hepatitis B Immune Globulin**

Hepatitis B immune globulin (HBIG) is derived from preselected human plasma and has a high titer (1:100,000) of anti-HBs. HBIG can be used to passively transfer antibodies to susceptible individuals who have had a significant exposure to a person known to have hepatitis B. A two-dose regimen of HBIG administered after accidental percutaneous exposure is about 75 per cent effective in preventing hepatitis B.<sup>35</sup> Because HBIG provides temporary immunity, it is indicated for health care workers only in certain post-exposure settings (Table 5). Since all contacts with patients capable of transmitting HBV are not recognized, it is unwarranted for health care workers to use HBIG as the only strategy for preventing occupationally acquired hepatitis B. Although some lots of HBIG contain antibody to HIV,<sup>64</sup> there is no evidence that HIV has been transmitted by HBIG.<sup>15</sup> Since all anesthesia personnel should receive hepatitis B vaccine, the use of HBIG should become less common in this group.

### **Hepatitis B Vaccines**

In the United States there are currently two licensed hepatitis B vaccines, plasma derived and recombinant.<sup>19</sup> The first vaccine, available since 1982, is prepared from the 22-nm spherical particles of HBsAg found in the plasma of chronic carriers of HBV.<sup>12, 46</sup> The antigen particles are purified by ultracentrifugation and then undergo biochemical inactivation using 8M urea, pepsin at pH 2, and 1:4000 formalin. These procedures have been shown to inactivate all known infectious agents including HIV, the virus responsible for AIDS.<sup>32</sup> Because plasma used to produce this vaccine was derived from

**Table 5.** *Recommendations for Hepatitis B Prophylaxis Following Percutaneous Exposure*

| SOURCE         | EXPOSED PERSON                                                                          |                                                                                                                                                              |
|----------------|-----------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                | <i>Unvaccinated</i>                                                                     | <i>Vaccinated</i>                                                                                                                                            |
| HBsAg-positive | 1. HBIG $\times$ 1 immediately*<br>2. Initiate HB vaccine series*                       | 1. Test exposed person for anti-HBs*<br>2. If inadequate antibody, HBIG $\times$ 1 immediately plus HB vaccine booster dose*                                 |
| Known source   |                                                                                         |                                                                                                                                                              |
| High risk      |                                                                                         |                                                                                                                                                              |
| HBsAg positive | 1. Initiate HB vaccine series<br>2. Test source for HBsAg; if positive, HBIG $\times$ 1 | 1. Test source for HBsAg only if exposed is vaccine nonresponder; if source is HBsAg positive, give HBIG $\times$ 1 immediately plus HB vaccine booster dose |
| Low risk       |                                                                                         |                                                                                                                                                              |
| HBsAg positive | Initiate HB vaccine series                                                              | Nothing required                                                                                                                                             |
| Unknown source | Initiate HB vaccine series                                                              | Nothing required                                                                                                                                             |

\* References 19 and 41 as well as current recommendations should be consulted for details on doses and acceptable antibody titers.

*Modified from Centers for Disease Control.*

chronic HBV carriers, some of whom were also in high-risk groups for HIV infection, there was concern by some that AIDS might be transmitted by this vaccine. This has now been disproved by several lines of evidence including lack of HIV antibody formation in vaccine recipients,<sup>41</sup> lack of HIV nucleic acids in the hepatitis B vaccine,<sup>32</sup> demonstration that HIV is inactivated by each of the biochemical purification steps,<sup>32</sup> and epidemiologic surveillance of vaccine recipients.<sup>18</sup>

A genetically engineered hepatitis B vaccine was licensed in 1986. Using recombinant technology, the gene for HBsAg was inserted into common baker's yeast.<sup>29</sup> Significant quantities of HBsAg for the vaccine would then be produced by the yeast. HBsAg is harvested by lysing the yeast cells and separating the viral antigen from the majority of the yeast protein and all of its DNA.

Both vaccines are administered intramuscularly in a three-dose series: the first injection is followed 1 month later by the second, and the third is given 6 months after the first. After the three-dose regimen, the antibody response in healthy, young adults is about 95 per cent with both the plasma derived (20  $\mu$ g per dose)<sup>27</sup> and the recombinant (10  $\mu$ g per dose) vaccines.<sup>65, 44</sup> (Other hepatitis B vaccines are under development, and the recommended doses and method of administration may differ. Specific literature for each vaccine should be consulted prior to its use.) There have been reports of lower rates of seroconversion in healthy adults when the vaccine was improperly

stored or when it was not administered in the deltoid muscle.<sup>16</sup> A study comparing the immunogenicity of the plasma derived and recombinant vaccines in homosexual men demonstrated that the seroconversion rate after the plasma-derived vaccine was higher (88 versus 74 per cent).<sup>56</sup> The response rate, which was lower than that reported in healthy, heterosexual adults, appeared to be the result of alteration of the immune system from HIV infection.

When tested in a large group of homosexual males, the plasma-derived vaccine was shown to be highly effective in preventing hepatitis B.<sup>76</sup> A similar large scale study of the efficacy of the recombinant vaccine in adults has not been performed, but animal data and use in neonates born to mothers who were HBV carriers suggest that it is comparable to the plasma-derived vaccine.

Several clinical studies have confirmed the safety of the vaccines.<sup>27, 65</sup> Neither vaccine contains intact HBV, and the recombinant product is made without the use of human or animal blood or blood products. Mild side effects ranging from soreness at the site of injection to fever, headache, or fatigue have occurred in 20 to 30 per cent of vaccine recipients.<sup>27, 81</sup> There have been no reports of serious side effects attributable to the vaccines, and epidemiologic surveillance has not found any link between the plasma-derived vaccine and adverse neurologic events.<sup>69</sup>

Since the plasma-derived vaccine has been in use for several years, there is now data to evaluate the need for booster doses in previously vaccinated individuals.<sup>4, 36</sup> Although the serum level of anti-HBs declines from peak levels after vaccination, protection against clinical hepatitis B persists for at least 5 years.<sup>36</sup> The duration and level of antibodies are directly related to the peak antibody titer after the third dose of vaccine.<sup>36, 43</sup> Although the risk of HBV infection is greater when the serum level of anti-HBs is low or undetectable, the resulting infection is subclinical and does not produce liver inflammation or a chronic carrier state.<sup>36</sup> Based on current data, booster doses of vaccine are not routinely recommended for healthy adults when vaccine has been properly administered.<sup>19</sup> The CDC is continuing to assess data related to the need for booster doses of vaccine and will update their recommendations as warranted.

Since properly administered hepatitis B vaccine produces antibodies in about 95 per cent of healthy adults, CDC does not recommend routine postvaccination testing for anti-HBs in this group.<sup>19</sup> An exception to this is made for individuals who initially received the vaccine in the buttocks.<sup>16</sup> It is recommended that antibody titer be measured in this situation and that those with low or undetectable levels undergo revaccination. Some hospital programs have chosen to perform postvaccination antibody testing to document that all health care personnel working in high-risk clinical situations have immunity to HBV infection. If this is done, interpretation of the antibody results may be difficult when the testing is performed more than 6 months after vaccination, that is, does a negative anti-HBs level mean that the individual did not respond to the vaccine (nonresponder) or that they

had an acceptable response initially and the titer subsequently declined to an unmeasurable level? Nonresponders remain at risk for clinical HBV infection<sup>11</sup> whereas persons who previously had sufficient antibodies are likely to have persistence of immunologic memory and still have protection against clinical infection. Programs electing to perform routine postvaccination testing should assess vaccinated persons within 6 months after the primary series. Usually, additional doses of vaccine are offered to nonresponders and hyporesponders in an attempt to stimulate antibody production. Revaccination of nonresponders with up to three additional doses results in adequate antibody levels in 30 to 50 per cent.<sup>75, 79, 80</sup>

The Immunization Practices Advisory Committee has recommended hepatitis B vaccine as preexposure prophylaxis for all health care workers at high risk for HBV infection (including anesthesia personnel).<sup>15</sup> Active immunization (vaccination) is the primary strategy for prevention of hepatitis B in health care workers. Most hospitals have developed programs for vaccinating moderate- and high-risk health care workers, and generally there has been a 40 to 50 per cent acceptance rate for the vaccine.<sup>23</sup> In a survey conducted in 1985, the vaccination rate in a group of medical residents at one institution was only 46 per cent.<sup>37</sup> Because the risk of HBV infection for trainees increases at the time that they begin to have contact with patients, medical students should be vaccinated prior to clinical rotations.<sup>57</sup>

Pregnancy is not a contraindication for hepatitis B vaccination since the hepatitis B vaccines do not contain infectious agents.<sup>19</sup> A prospective study has demonstrated that vaccination of pregnant women is both safe and effective.<sup>3</sup>

Additional hepatitis B vaccines are under development.<sup>82</sup> It is hoped that an effective vaccine can be produced at a low cost so that it will be economically feasible to vaccinate large populations in areas of the world where hepatitis B is endemic.

### **Postexposure Prophylaxis Strategies**

The CDC has published recommendations for treatment of health care workers who have experienced percutaneous or accidental needlestick exposure to blood, body fluids, or tissues that may be infectious for hepatitis B.<sup>19, 41</sup> The suggested treatment depends on the likelihood of HBsAg positivity of the source and the anti-HBs status of the exposed individual (see Table 5). In individuals without immunity, the risk of HBV infection after an exposure to HBsAg positive blood through an accidental needlestick is at least 20 per cent<sup>68</sup> and may be as high as 30 per cent.

The Immunization Practices Advisory Committee is presently considering changes in their recommendations for follow-up treatment of health care workers after accidental needlesticks. These may occur in two areas: (1) all source patients may be tested for HBsAg regardless of their likelihood of being a HBV carrier; and (2) only nonvaccinated personnel or those without previously demonstrable

anti-HBs would receive prophylaxis. Current recommendations should be consulted.

### **Prenatal Screening and Immunization of Pregnant Women**

Children of HBsAg-positive women are at increased risk of HBV infection at birth and are likely to become chronic carriers of the virus. Studies have demonstrated that the administration of HBIG and hepatitis B vaccine to these high-risk infants shortly after birth is effective in preventing HBV infection.<sup>74</sup> An analysis of the costs of prenatal screening of all pregnant women in the United States for HBsAg and immunization of the neonates at risk for HBV infection suggests that institution of this as a national policy would be extremely cost-effective.<sup>2</sup> The Immunization Practices Advisory Committee of the U.S. Public Health Service has now recommended that all pregnant women should be routinely tested for HBsAg early in the prenatal period, and that infants born to HBsAg positive mothers should receive HBIG and hepatitis B vaccine.<sup>40</sup>

## **TYPE D (DELTA) HEPATITIS**

Delta hepatitis occurs only in the presence of active HBV infection. Although it is transmitted as an independent infectious agent, the hepatitis D virus (HDV) is defective in that it can replicate only with the help of HBV. Therefore, it produces either a coinfection with acute hepatitis B or a superinfection in chronic HBV carriers.<sup>39</sup>

### **Hepatitis D Virus**

HDV is a 35-nm particle that consists of an outer coat of HBsAg (produced from the genome of the HBV helper virus) surrounding an internal delta antigen (HD Ag) and a small, circular RNA molecule (see Table 1). The structure and mode of replication of HDV are unlike any other known animal viruses.

### **Hepatitis D Virus Infection and Serologic Markers**

Delta hepatitis was first recognized in Italy in 1977 when HD Ag was discovered in liver biopsy samples from patients who were chronic HBV carriers.<sup>61</sup> Like hepatitis B, delta hepatitis exists in acute and chronic forms but in general, the clinical disease tends to be more severe. Acute delta hepatitis may occur as a coinfection, the simultaneous presence of acute hepatitis B and acute delta infection, or as a superinfection, acute delta infection in a chronic HBV carrier. With acute coinfection, HD Ag is present along with HBsAg during the incubation stage prior to the onset of clinical symptoms (see Table 2). (Currently, tests for measuring HD Ag in the serum are not commercially available.) Acute delta coinfection is usually a self-limited disease with less than 5 per cent of patients developing chronic HDV infection. Resolution of the acute infection is marked by the appear-

ance of antibody to HD Ag (anti-HD) in the serum. This is followed by the loss of HBsAg seropositivity and the production of anti-HBs.

When acute delta superinfection occurs in chronic HBV carriers, about 80% go on to have chronic hepatitis. Since these patients have persistence of HBsAg, they are less likely to have resolution of the HDV infection. Chronic HDV infection can be diagnosed by the continued presence of HBsAg and anti-HD seropositivity.

The mortality rate of acute delta coinfection ranges from 1 to 10 per cent whereas that of acute superinfection is reported to be 5 to 20 per cent. The typical clinical course of patients with chronic HDV infection is worse than those with chronic hepatitis B. In contrast to the 15 to 30 per cent rate of cirrhosis in patients with chronic hepatitis B, chronic HDV infection is usually more aggressive and results in a significantly higher percentage who develop cirrhosis.

### **Epidemiology of Hepatitis D Virus Infection**

Because HDV infection occurs only in individuals actively infected with HBV, the epidemiology of the two viruses is linked. Delta hepatitis is endemic in certain areas of the world with a high prevalence reported in the Middle East, Southern Italy, Northern Africa, and some Indian populations of South America.<sup>58</sup> Epidemic outbreaks of delta hepatitis have occurred in other areas.<sup>50</sup> Delta hepatitis is rare in the general population of the United States; however, in groups that have a high infection rate with HBV, it makes a significant contribution to the sequelae of chronic hepatitis or cirrhosis. A survey of cohorts of homosexual men in four U.S. cities demonstrated a range of anti-HDV seroprevalence to be 0 to 15 per cent.<sup>73</sup>

HDV is a blood-borne virus and can be transmitted by parenteral and nonparenteral routes. In areas where delta hepatitis is endemic, transfusion of blood infected with HDV has been documented.<sup>63</sup> Nosocomial transmission of HDV to a surgeon has been reported.<sup>49</sup>

Immunity to HBV, from either previous resolved infection or vaccination, prevents HDV infection. Thus, health care workers who have acceptable titers of anti-HBs after receiving hepatitis B vaccine are also protected against delta hepatitis.

### **NON-A, NON-B HEPATITIS**

When serologic tests became available in the 1970s for diagnosis of hepatitis B, it was recognized that there was another hepatotropic virus distinct from HBV or HAV that was responsible for the majority of cases of post-transfusion hepatitis. Over the ensuing decade much has been learned about this distinct form of viral hepatitis that is called non-A, non-B hepatitis (NANB).<sup>25</sup> Post-transfusion NANB hepatitis was thought to be caused by two different NANB viruses, NANB hepatitis is transmitted by both percutaneous and nonpercutaneous routes, and there is a distinct epidemic form of NANB that has an

epidemiology similar to hepatitis A. Study of the disease had been hampered because researchers had been unable to isolate and identify the infectious agents responsible for NANB and no specific diagnostic tests are commercially available. The diagnosis of NANB hepatitis must be made clinically by excluding other infectious causes of hepatitis in patients having the appropriate clinical picture for the disease. There have been recent reports that a virus responsible for the post-transfusion form of NANB has been identified,<sup>22</sup> part of the viral genome has been cloned, and a potentially useful clinical test for the virus is being developed.<sup>48</sup> The virus has been difficult to isolate because only small numbers are present in the blood of infected patients.

### **Epidemiology of the Post-transfusion Form of Non-A, Non-B Hepatitis**

Most cases of NANB hepatitis are sporadic and without known etiology. About 15 per cent occur after blood transfusion and about 90 per cent of post-transfusion hepatitis is NANB. Several strategies have been introduced to reduce the incidence of post-transfusion NANB hepatitis, and these are covered in another article in this volume.

In some respects, the epidemiology of NANB is similar to that of hepatitis B. NANB has been documented after treatment with pooled blood products including coagulation factors. Annual attack rates of 2 to 6 per cent have been reported in hemophiliacs who have required multiple transfusions. Sporadic cases of NANB have occurred in users of illicit intravenous drugs. NANB has become the most frequent cause of hepatitis in patients and staff of dialysis units since the introduction of effective guidelines to prevent hepatitis B. It appears that perinatal transmission of NANB may occur from acutely infected women to the newborn.

Occupationally related spread of NANB has occurred in health care workers, and although the frequency of this is unknown, it is thought to be rare. In one report, a medical student developed NANB hepatitis 8 weeks after an accidental puncture with a needle that had been used on a kidney-transplant recipient.<sup>53</sup> In a group of Danish nurses, 38 per cent of cases of hepatitis that occurred after employment were not associated with serologic markers for HBV or HAV and presumably were caused by NANB, but alcohol-induced liver enzyme elevation could not be ruled out.<sup>72</sup>

In homosexual men, the incidence of NANB is less than for hepatitis B. Heterosexual transmission of NANB from patients with post-transfusion hepatitis to their partners is rare. These data suggest that sexual transmission of NANB is less efficient than HBV.

Approximately 25 per cent of cases of sporadic acute hepatitis in the United States are due to NANB. Since up to half of these patients are unable to document or fail to remember any percutaneous exposure, there may be nonpercutaneous mechanisms for transmission of NANB.

## Clinical Disease

The mean incubation period for post-transfusion NANB is 7 to 8 weeks. Generally, acute NANB is clinically less severe than hepatitis A or B. Symptoms of hepatitis are not as debilitating, liver enzymes are only moderately elevated, and only 25 per cent of patients develop jaundice. NANB is characterized by fluctuating serum aminotransferase levels. Fulminant acute NANB hepatitis is rare.

Although the clinical picture of the acute post-transfusion form of NANB is benign, almost 50 per cent of patients have persistent or fluctuating aminotransferase elevations for more than 6 months. Clinical follow-up of patients with acute NANB indicate that they are very likely to develop chronic hepatitis or an asymptomatic carrier state. It is now felt that most cases of nonalcoholic cirrhosis in the United States are due to the post-transfusion form of NANB. In a group of patients with chronic NANB hepatitis after transfusion, 60 per cent had chronic active hepatitis, cirrhosis, or both on liver biopsy. Chronic NANB is more likely after transfusion or percutaneous transmission than in sporadic cases. Some individuals may become asymptomatic carriers after acute NANB, and it has been estimated that the prevalence of asymptomatic NANB carriers in the United States may be as high as 3 to 7 per cent. Like hepatitis B, chronic NANB may be linked to hepatocellular carcinoma, but this has been difficult to prove because of the inability to test for specific serologic markers and because a definitive causative agent for the disease has only recently been identified.

There is also no specific clinical tests for a serologic marker for the infection. It is possible that the antibody to the infectious agent is not present in the serum or occurs at such a low concentration that it is undetectable by current methods. Indirect "surrogate" tests (ALT and anti-HBc) have been used to screen donated blood for NANB.

Currently, there are no specific therapies that have been shown to be effective for treatment of acute or chronic NANB and no immunization for prevention. These will likely have to await better characterization of the causative agent. Immune globulin has been recommended by some after nontransfusion, percutaneous or nonpercutaneous exposure (accidental needlesticks, sexual, perinatal), but the effectiveness has not been documented.<sup>41</sup> Several clinical trials have demonstrated that hepatitis B immune globulin does not prevent NANB hepatitis.

## Epidemic Form of Non-A, Non-B Hepatitis

In North America and Western Europe there have been no epidemics of NANB hepatitis, and transmission appears to be similar to that of hepatitis B. In contrast, there have been outbreaks of NANB in Asia, spreading by waterborne or fecal-oral mechanisms. This epidemic form of NANB has several characteristics: it most commonly affects young, adult males; has an incubation period of about 40 days; has a high fatality rate, especially in pregnant women; and is unlikely to progress to chronic liver disease.

In one outbreak of epidemic NANB, 27-nm virus-like particles were isolated from the stools of infected patients.<sup>45</sup> Inoculation of four marmosets with these particles resulted in hepatitis in three and antibody production in one. This virus has undergone serial passage and has remained infectious for test animals. Most investigators have accepted this virus as the agent responsible for the epidemic form of NANB. Further characterization of the virus is underway.

## CONCLUSION

Over the past 25 years, the growth of knowledge in the area of viral hepatitis has resulted in the understanding of the epidemiology and modes of transmission of the agents responsible for these diseases, in specific laboratory tests to diagnose some of these infections, and in vaccines to immunize against HBV infection. Since they are at an increased risk for occupationally acquired hepatitis, anesthesia personnel must be aware of this information so that they can incorporate it into their work practices.

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## **Human Immunodeficiency Virus Infection**

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This review defines the biology of human immunodeficiency virus type 1 (HIV-1), outlines clinical and epidemiologic patterns of HIV-1 infection, and comments on current preventive and palliative therapeutic approaches to HIV-1 infection and transmission. We discuss risk of HIV-1 transmission in medical settings between patients and health care workers. In addition, pathogenic retroviruses other than HIV-1 will be described and their clinical features delineated.

### **THE BIOLOGIC FEATURES OF HIV-1**

HIV-1 is a retrovirus, a class of viruses whose replication depends on the flow of genetic material from RNA to DNA. This passage of material is the reverse of the usual transfer of genetic information and is made possible by reverse transcriptase, a special viral DNA polymerase. Retroviruses had been postulated since early in this century, but their reproductive biology was unknown until the discovery of reverse transcriptase in 1970.<sup>4, 56</sup> With the recognition of the disease complex of infectious immunosuppression (AIDS) in the early 1980s and its etiologic association with the HIV-1 retrovirus, retroviral research exploded. In the initial studies, many principles of the biology and life cycle of retroviruses were established. Thereafter, progress has continued steadily, but more slowly, as scientists search for therapeutic methods to manipulate or alter the HIV-1 life cycle to control disease spread or progression.

HIV-1 is not a single well-defined virus type but represents a large family of highly divergent subtypes. Variations exist in nucleotide sequences, as well as biological properties such as replication rate

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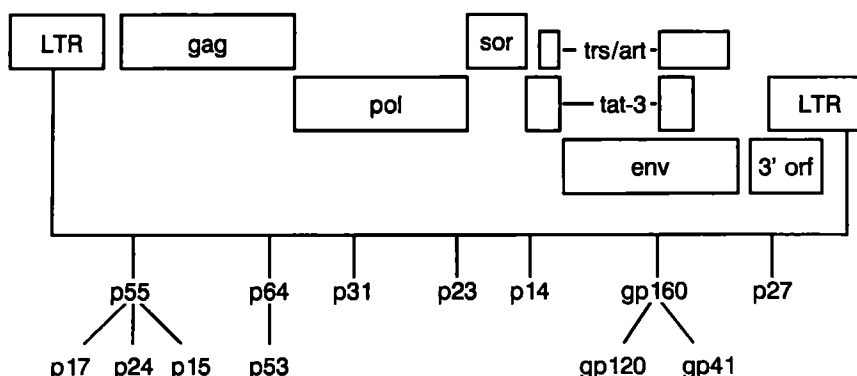


Figure 1. Typical HIV-1 genome. There are nine genes identified thus far. Three genes encode structural components (gag, env, and pol genes); the others are regulatory. LTRs are long terminal repeats that initiate the other genes. The gag and env genes encode HIV-1 core (p 17, p 24, p 15) and envelope (gp 120, gp 41) structural proteins, respectively. The pol gene encodes reverse transcriptase. Abbreviations: p = proteins, gp = glycoproteins, numerics = molecular weight in kilodaltons.

and cytopathic effects.<sup>31, 37</sup> In general, the HIV-1 genome includes at least nine genes.<sup>27</sup> These genes may regulate synthesis of structural proteins, repress or activate production of regulatory proteins, or participate in both functions (Fig. 1). The gag, pol, and env genes are common to all retroviruses and encode structural proteins, the antigens involved in the host's production of antibodies to HIV-1. The gag and env genes encode structural proteins of the virus core and envelope, respectively. The pol gene encodes reverse transcriptase.

HIV-1 structure consists of an outer envelope, a core outer component, and RNA and reverse transcriptase within the core (Fig. 2). These structures are composed of proteins (p) and glycoproteins (gp) of different molecular weights, expressed in kilodaltons. For example, one envelope molecule is labeled gp 41 (glycoprotein of approximate 41 kd weight). These proteins have unique functions and antigenic properties.

HIV-1 replication begins when an HIV-1 particle binds to the outside of a cell (Fig. 3).<sup>31</sup> Binding depends on an interaction between a molecule on the membrane of the cell (CD4) and the viral envelope molecules gp 120 and gp 41. This interaction leads to fusion of the viral and cell membranes. The viral core enters the cell directly by either fusion or endocytosis. The CD4 receptor is found on many cell types, including T-cell lymphocytes (T4 lymphocytes), monocytes, macrophages, glial cells, chromaffin cells in the gut, some lymph nodes, skin, rectal mucosal cells, and a small number of B-cell lymphocytes.<sup>7</sup> Once inside the cell, the viral genomic RNA is free of its core membrane and is converted to DNA. This conversion is facilitated by reverse transcriptase. The result of this conversion is the duplication of RNA into a double-stranded DNA (the same molecular form

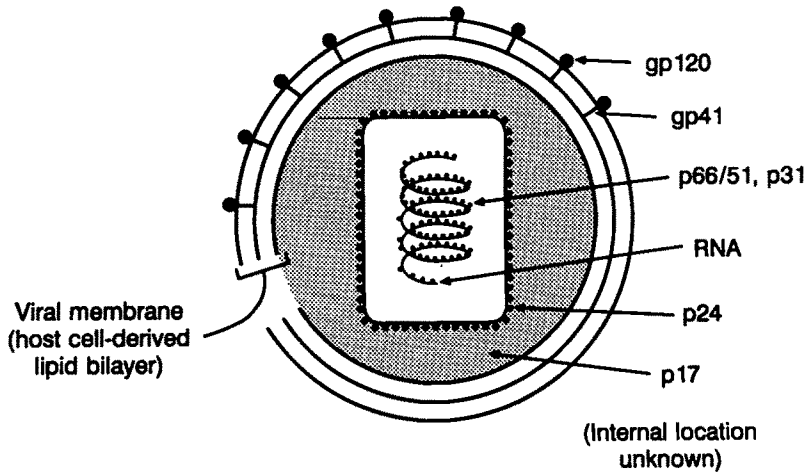


Figure 2. Schematic of HIV-1 structure and its antigens. The envelope consists of two glycoproteins, gp 120 and gp 41. The knobs of gp 120 are anchored into the envelope base of gp 41. These gp 120 knobs bind to CD4 receptors. The virus core includes p 24 and contains RNA and reverse transcriptase. (From Human Immunodeficiency Virus (HIV-1), Biotech/Dupont HIV-1 Western Blot Kit, DuPont Co., Wilmington, DE.)

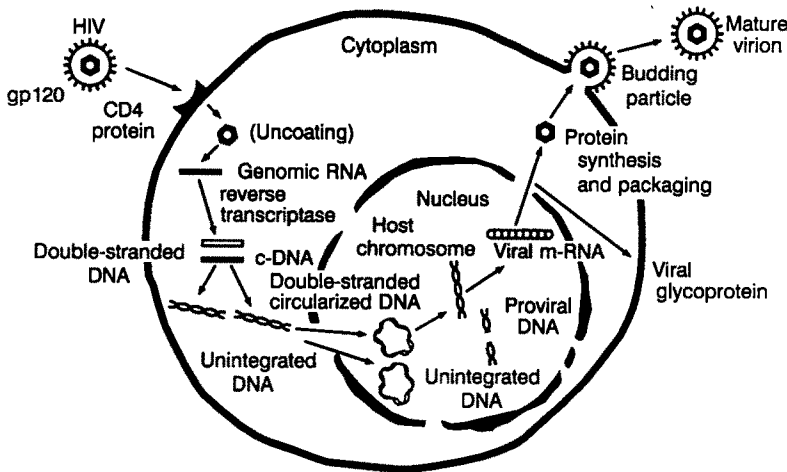


Figure 3. Replication of HIV-1 in a cell with CD4 receptor molecules. See text for discussion. (From Groopman JE, Gurley J: Biology of HIV-1 infection. In AIDS: Information on AIDS for the Practicing Physician, vol 2. Chicago, American Medical Association, 1987 p 17; with permission).

used by the cell to carry its own genes). The new DNA carries the viral genetic information and is either integrated with the host-cell's DNA or left unintegrated. If integrated, the new DNA contains both cellular and viral genetic material and is called proviral DNA. Proviral DNA may lie dormant for prolonged periods and not encode viral proteins, but it will be duplicated every time the cell divides and reduplicates. At this point, the cell is permanently infected.

Proviral DNA may rest in quiescent cells. In some cells, however, unknown mechanisms trigger the production of infectious viral particles. Once triggered, the viral segment of the proviral DNA directs production of viral structural proteins and enzymes. Once produced, these proteins, RNA, and enzymes are packaged into particles, or new virions. In one final step, the virion buds as a mature virus from the cell membrane, enclosed in its envelope protein.

Cell death from HIV-1 infection may occur in several ways.<sup>49</sup> The unintegrated viral DNA may be directly toxic. The viral envelope gp 120 and gp 41 may bind to CD4 molecules on the infected cell's membrane while budding from it, tearing holes, and causing cell swelling and death. The viral envelope glycoproteins may also bind and fuse more than one cell. Many cells can fuse, mediated by CD4 molecules, into giant, unsurvivable syncytia. Finally, the envelope proteins may indirectly cause cell death by initiating an immune response to produce antibodies. The resultant antibodies may not eliminate or inactivate the virus, possibly because sugar molecules on the viral envelope prevent antibody binding. Instead, these antibodies can bind to cells of the body that may have bound free-floating gp 120. Once bound, these antibodies activate complement to lyse the antibody-covered cell. Complex interactions between other viral and cellular proteins may also be contributory to various immune system changes and affect cell survival.

## CLINICAL CHARACTERISTICS OF HIV-1 INFECTION

When first identified as a new, unique disease complex with no identifiable etiologic process, AIDS represented a cluster of unusual infectious diseases and cancers that occurred in homosexual men. For epidemiologic and surveillance purposes, a specific definition of AIDS was adopted by the Centers for Disease Control (CDC) and was revised in 1987.<sup>12, 13</sup> This restriction on acceptance of cases as AIDS provided a core of patients for investigation. This permitted rapid identification of an etiology (HIV-1), epidemiologic insight, and knowledge of the end stage of the infectious process. It failed, however, to promote understanding of the HIV-1 disease spectrum.

HIV-1 infection is a variably progressive disease that may result, in many cases, in AIDS and death (Table 1). Its speed of progression and severity of accompanying illnesses are dependent on many underlying factors, including extent of initial exposure.<sup>37</sup> In general, however, the disease progresses concurrent with a steady, gradual rise

**Table 1.** *Generally Accepted Characteristics of HIV Infection*

- 
- There is a brief acute illness, followed by chronic infection that can be transmitted.
  - HIV infection is often subclinical and unrecognized for years.
  - Once clinically evident, HIV infection is progressive and causes severe immunologic deficiencies
  - Opportunistic infections and unique cancers are the hallmark of the full-blown infection (AIDS)
- 

in the amount of virus in the blood.<sup>49</sup> The greater the amount of virus present, the more severe and faster the progression of HIV-1 infection.

This steady progression is the basis for the Walter Reed classification system of HIV-1 infection into six stages from exposure (stage 0) to AIDS (stage 6), with markers of immunologic dysfunction and clinical disease that reflect the abnormalities of the immunologic system.<sup>50</sup> The key marker of immune function in this classification system is depletion of T4 lymphocytes to less than 400 cells per cubic millimeter. The T4 lymphocyte is vital to initiation of the immune response as the sentinel that recognizes foreign antigens on infected cells.<sup>49</sup> Once stimulated, it activates the immune response by signaling B lymphocytes to multiply and produce appropriate antibodies. It also propagates the cell-mediated killing response of T8 lymphocytes and white cells and scavenging activity of monocytes and macrophages.

The progression of the clinical spectrum of HIV-1 infection varies among individual patients. From initial exposure until the immune system develops an adequate response, individuals may be highly infectious (Fig. 4). Once the host's response develops, further viral replication is slowed but over an extended period enough HIV-1 are present to overpower the immune response and proliferate unchecked. Infected individuals again become highly infectious. With T4 lymphocyte depletion, opportunistic bacteria, fungi, and viruses are likely to produce frequent infections.

### Identification of HIV-1 Infection

The presence of HIV-1 is detected by viral culture or by serologic identification of either HIV-1 antigen or antibodies to HIV-1. Culture identification of HIV-1 has been difficult and insensitive. The proportion of individuals with AIDS who are HIV-1 culture positive at any specific sampling time varies.<sup>1, 18, 38, 51</sup> The culture is a technically difficult procedure. Because the virus is usually found in cells, viremia can be intermittent and of variable quantity.

Serologic tests for either antibodies to HIV-1 or HIV-1 antigen are more commonly used to identify HIV-1 infection. Serologic tests for antibodies to HIV-1 detect those antibodies produced by the infected host in response to antigenic proteins of the virus. Tests that are now available are shown in Table 2. These tests vary in their sensitivity and specificity to detect antibodies to HIV-1 core, enve-

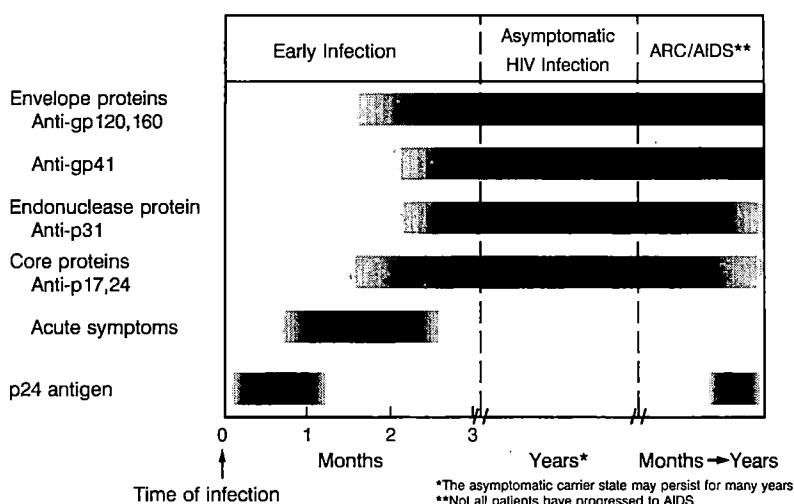


Figure 4. Usual time course of serologic responses. Within 1 to 2 weeks of initial exposure, p 24 antigen may be detected. Normally, p 24 antigen becomes undetectable within 1 month of exposure, possibly from neutralization by p 24 antibody. Acute flu-like symptoms may appear transiently at 1 month. The remaining antibodies become detectable at approximately 6 to 12 weeks. HIV-1 infected individuals may be asymptomatic for prolonged periods. In some individuals who progress to AIDS, p 24 antigen once again may become detectable, a poor prognostic indication that HIV-1 is overwhelming the immune response. (Modified from Steckelberg JM, Cockerill FR: Serologic testing for human immunodeficiency virus antibodies. Mayo Clin Proc 63:373-380, 1988; with permission.)

lopes, and regulatory proteins. The enzyme-linked immunoassay (ELISA) is a highly sensitive screen for HIV-1 antibodies in plasma (Fig. 5). Because it is inexpensive and very reproducible, it is the primary screening test for the presence of HIV-1 antibodies. It is possible, however, for other cellular proteins, plasma from patients with other immunologic abnormalities, and antibodies to anti-HLA DR4 to cross-react with the antigens used in the ELISA test and result in false-positive findings.<sup>54</sup> Therefore, the more specific Western blot immunophoresis is commonly used to confirm positive ELISA tests (Fig. 6). The Western blot is very specific, but because criteria for positive responses are occasionally unclear, repeat testing or the use of other

**Table 2. HIV Tests: Serologic Tests for Antibodies**

|                                         |
|-----------------------------------------|
| Enzyme-linked immunoassay (ELISA)       |
| Western blot immunophoresis             |
| Radioimmunoprecipitation                |
| Cytoplasmic membrane immunofluorescence |
| Rapid latex agglutination               |

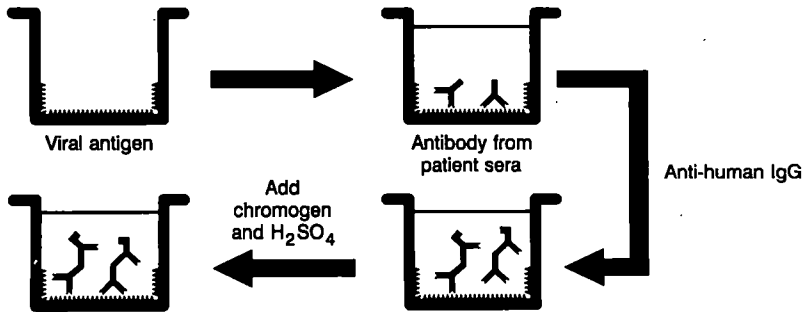


Figure 5. ELISA test for HIV-1 antibody in serum. Purified, inactivated virus is adsorbed onto the inner walls of a microwell. Serum is added to the well; if antibodies to the virus are present, they bind to antigen to form an antigen-antibody complex. Peroxidase-labeled anti-human immunoglobulin is added and binds to the antigen-antibody complex. Chromagen is added to produce a blue color proportional to the amount of antibody present. Sulfuric acid catalyzes an enzymatic reaction producing a color change to yellow. Optical absorbances of controls and test samples are determined with a spectrophotometer. The optical density defined as a positive result is determined by the manufacturer and may differ from one manufacturer to another. (From Human T-Lymphotropic Virus Type III, Genetic Systems LAV EIA, Genetic Systems Corp., Seattle, WA.)

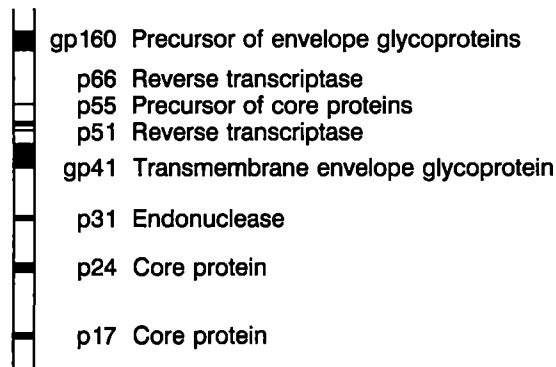


Figure 6. Western blot test for HIV-1 antibody in serum or plasma. Partially purified, inactivated HIV-1 virus is disrupted with detergent. Specific HIV-1 proteins are fractionated by electrophoresis onto a polyacrylamide slab gel and transferred to a nitrocellulose membrane strip. This strip is incubated with serum or plasma; if antibodies are present, they will bind to the antigens previously bound to the nitrocellulose strip. Specific antigen-antibody complexes are visualized as bands after incubation with anti-human immunoglobulin. The major HIV-1 bands are depicted. Abbreviations: gp = glycoproteins, p = protein, numerics = molecular weight in kilodaltons. (From Human Immunodeficiency Virus [HIV-1], Biotech/Dupont HIV-1 Western Blot Kit, DuPont Co., Wilmington, DE.)

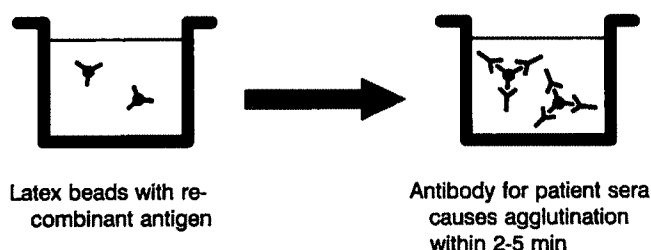


Figure 7. Rapid latex agglutination test for HIV-1 antibody in serum. Latex beads coated with recombinant HIV-1 envelope polypeptide (Cambridge BioScience Corp.) are mixed with serum. If present, antibodies to HIV-1 envelope proteins form antigen-antibody complexes and agglutinate within 2 to 5 minutes. The test is rapid, simple to learn and perform, stable at room temperature, and reproducible.<sup>48</sup>

tests may be necessary to confirm the presence of HIV-1 antibodies. In fact, cytoplasmic membrane immunofluorescence (IFA), as well as the Western blot, are routinely used by health officials of California to confirm a positive ELISA.

Rapid latex agglutination detects HIV-1 antibodies and, like ELISA, is used as an initial screening test (Fig. 7).<sup>29, 48</sup> It was developed for use in blood banks for rapid screening in nonindustrialized countries where facilities, technicians, or equipment to perform ELISA or Western blot tests may not exist. The ELISA test takes most of 1 day; latex agglutination can be completed within 10 minutes. This time savings is essential in areas without refrigeration where blood donation and transfusion must occur within several hours. The sensitivity and specificity of ELISA and latex agglutination tests in populations of North America have not yet been compared.

## EPIDEMIOLOGY

With few exceptions, HIV-1 is transmitted by blood, sexual intercourse, and from mother to child.<sup>23</sup> This information, therefore, should limit its spread. Indeed, the risk of transfusion-transmitted HIV-1 infection has become negligible in developed countries where donor screening and unit testing has been implemented.<sup>59</sup> Specific high-risk groups, especially the North American homosexual male population, have reduced the rate of spread of infection by educational programs that advocate avoidance of high-risk sexual practices.<sup>45, 57</sup>

In other groups, however, HIV-1 infection continues to spread exponentially.<sup>2, 28</sup> Most nonindustrialized nations have been unable to limit HIV-1 transmission.<sup>21, 39</sup> Insufficient equipment, supplies, and trained personnell have limited pretransfusion screening of blood. Prevention of perinatal transmission requires mass screening to identify HIV-1 infection in women of childbearing age, a program too ex-

**Table 3.** *Cases of AIDS Reported (CDC Surveillance Report, February 6, 1989)*

| TRANSMISSION CATEGORY                | CUMULATIVE NO. | PER CENT |
|--------------------------------------|----------------|----------|
| Adults                               |                |          |
| Homosexual/bisexual male             | 51,922         | 62       |
| IV drug user                         | 16,805         | 20       |
| Homosexual male/drug user            | 6,050          | 7        |
| Heterosexual                         | 3,718          | 4        |
| Transfusion (nonhemophiliac)         | 2,098          | 3        |
| Transfusion (hemophiliac)            | 807            | 1        |
| Undetermined                         | 2,790          | 3        |
| Subtotal                             | 84,190         |          |
| Children                             |                |          |
| Parent with/at risk of HIV infection | 1,087          | 78       |
| Transfusion (nonhemophiliac)         | 175            | 13       |
| Transfusion (hemophiliac)            | 84             | 6        |
| Undetermined                         | 54             | 3        |
| Subtotal                             | 1,400          |          |
| Combined total                       | 85,590         |          |

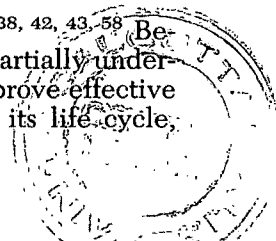
pensive to be feasible. Even when HIV-1 status is known, cultural factors may limit approaches to contraception and termination of pregnancy.

These and other problems are found in industrialized countries. Reducing the incidence of HIV-1 transmission between intravenous drug users will be difficult for many reasons including resistance to educational programs.<sup>23</sup> Perinatal transmission of infection occurs predominantly from mothers who are intravenous drug users or who have infected sexual partners.<sup>2, 52</sup>

In the United States, epidemiologic surveys indicate that there are two main exposure categories responsible for the majority of adult AIDS cases; male homosexuals and intravenous drug users (Table 3).<sup>28</sup> Estimates by most authorities suggest 1.25 to 2 million people in the United States are infected with HIV-1. The incidence of HIV-1 infection appears to be leveling for homosexual men and rising for intravenous drug users. The incidence is also rising for children of infected mothers. Nearly 1 per cent of all newborns in New York City are seropositive.<sup>2, 36</sup> Of these, it is estimated that approximately 20 per cent will develop AIDS in the first year of life.

### **THERAPEUTIC APPROACHES TO PREVENTION AND SUPPRESSION OF HIV-1 INFECTIONS**

There are few effective antiretroviral drugs.<sup>30, 32, 38, 42, 43-58</sup> Because the specific mechanisms of HIV-1 infection are partially understood, it may be possible to design therapies that will prove effective in various segments of its replication. The nature of its life cycle,



however, makes it particularly difficult to treat. HIV-1 integrates with the host cells' genomes and may be inactive for extended periods. A safe and effective therapeutic drug must, therefore, kill or attenuate the virus while destroying or damaging as few of the host cells as possible.

For now, zidovudine (azidothymidine, AZT, Retrovir) is the only drug available that is proven beneficial against HIV-1.<sup>30</sup> AZT inhibits transcription of HIV-1 RNA into DNA by blocking the linkage of nucleotides catalyzed by reverse transcriptase.<sup>58</sup> In AIDS patients, it is effective at improving survival, decreasing opportunistic infections, and improving dementia and functional capabilities.<sup>5, 15, 47</sup> AZT is toxic, particularly to the bone marrow. Macrocytic anemia and granulocytopenia are common during treatment with AZT. HIV-1 residing in monocytes/macrophages may be the primary modality for viral transmission between individuals.<sup>7</sup> If true, monocytes may be able to harbor HIV-1 and act as reservoirs during transmission of infectious particles.<sup>19</sup> Because AZT is not very effective in eliminating this reservoir, combinations of antiretroviral agents may be necessary. The National Institutes of Health AIDS Clinical Trials Group is investigating many different drugs and their combinations for synergistic, antagonistic, or additive effects against HIV-1.

Active immunization with a vaccine is the simplest and safest form of prevention for many viral diseases. Smallpox, polio, measles, mumps, and rubella have been controlled or nearly eliminated by very effective vaccine programs. The public expects, therefore, similar success with prevention of HIV-1. There are, however, several characteristics of HIV-1 infection that have made vaccine development difficult: the virus may be either free in the blood *and* incorporated into host cells; there may be multiple HIV-1 variants in infected individuals; there is no animal model for HIV-1 infection; and there are ethical considerations that may hinder the use of human volunteers in clinical trials.<sup>42, 43</sup>

Vaccines are effective when they stimulate the recipient's immune system to prevent infection by a pathogen. The host's immunologic memory will then be stimulated when it encounters a pathogenic antigen. Thereafter, the immune system responds with a humoral and cell-mediated response. Commonly, the cell-mediated immune response is activated by T4 lymphocytes. This is a major challenge for HIV-1 vaccine development; the virus infects and destroys the very cells needed to activate the cell-mediated immune response. Virologists are pursuing a number of strategies to design HIV-1 vaccines that overcome this obstacle.

HIV-1 has multiple strains and mutates rapidly. Different variants can be found in individuals. These variants occur after initial exposure and may adapt to their host with increased cytopathic activity and new cytotrophisms.<sup>32</sup> These mutations can cause marked differences in progression of symptoms and potential for transmission. Not surprisingly, subsequent viral variants may be uninhibited by the antibody response to the initial HIV-1 strain.<sup>20</sup>

Traditionally, human subjects are not used in biomedical research until adequate laboratory and animal experimentation has been performed. For HIV-1, there is no good animal model that manifests the progression of HIV-1 infection to AIDS. Although chimpanzees and gibbons can be regularly infected with HIV-1 and used in testing toxicity and immunogenicity of potential vaccines,<sup>16</sup> it is not clear if the immunologic responses of these primates are applicable to humans; they develop chronic HIV-1 infection, but do not develop symptoms of AIDS.

Because there is no good animal model, promising vaccines may have to be tested in humans. The ethical and logistic considerations of human testing without previous animal experimentation are complex. The goals of HIV-1 vaccine development are to prevent susceptibility, limit progression, and decrease severity of morbidity and mortality from infection. Logistically, only one of these, a vaccine's efficacy for preventing infection, can be addressed with several years of trials. Effectiveness against disease progression and outcome will require longer periods of evaluation of human research subjects. Importantly, who will volunteer? Volunteers should be well informed of the potential risks. At this time, the risks associated with new vaccines are unknown. It is presumed that vaccination will result in an antibody response; confidentiality of HIV-1 antibody status of these volunteers must be assured to protect them against discrimination by employers, insurers, and others. In addition, who is responsible for any harm incurred by these volunteers? In general in the United States, injuries incurred from research are not mandatorily compensated by researchers or drug sponsors.<sup>42</sup> The ethical considerations should be debated and resolved before clinical trials begin.

### IMPLICATIONS FOR ANESTHESIA PERSONNEL

In the setting of the operating room, intensive care unit, or emergency room, it is likely that anesthesia personnel will either knowingly or unknowingly provide care for patients with HIV-1 infection. The HIV-1 status will be known in those patients diagnosed as having AIDS and possibly in those with symptomatic HIV-1 infection and opportunistic infections. Exposures may occur to asymptomatic, non-diagnosed, HIV-1 infected patients who are having procedures not related to their infection. Because health care workers provide medical care to patients with HIV-1 infection and routine preoperative HIV-1 screening may not be ethically or logistically feasible, all patients should be treated as if they were carrying a blood-borne infection (universal precautions).<sup>34</sup> Emphasis should be placed on avoiding contact with potentially infectious blood and certain body fluids. In particular, needle-stick injuries present a significant risk of exposure to HIV-1 for anesthesia personnel. Precautions to prevent needle-stick injury must be routinely observed.

What procedures are most common in HIV-1 infected patients?

Three surgical procedures requiring anesthetic management in patients with AIDS are lymph node biopsy, splenectomy, and partial colectomy.<sup>53</sup> A lymph node biopsy may be performed for diagnosis of infection or tumor. Splenectomy may be required for autoimmune thrombocytopenia purpura unresponsive to AZT or corticosteroid therapy. Partial proctocolectomy or ileocolectomy is usually performed after bowel perforation from infectious cytomegalovirus colitis. Many patients with symptomatic HIV-1 infection will have esophagitis and dysphagia secondary to candidiasis or cytomegalovirus infection. Patients with these disorders often have gastric reflux and rapid sequence inductions may be warranted.

Anesthesia personnel may be asked numerous questions regarding the risk of HIV-1 transmission. Patients having routine, elective surgery will inquire about the safety of potential blood transfusions. (This subject is covered in another article in this issue.) Concern over transfusion-transmitted HIV-1 infection has dramatically affected transfusion practices and stimulated innovative blood-conservation techniques. The safety of the blood supply in North America is essential, and changes in donor selection and blood testing are important in the reduction in risk for HIV transmission through transfusion.

Our coworkers will ask about the risk of acquiring HIV-1 from our patients. Based on data from several epidemiologic surveys, the risk is extremely low.<sup>3, 9, 10, 22, 24, 41</sup> There are no reports of anesthesia personnel who have acquired HIV-1 infection from patient care. Documented transmission of HIV-1 infection to health care workers has occurred but usually this has followed prolonged exposure to blood from infected patients or an accidental needle-stick. Approximately 80 per cent of all occupationally related HIV-1 infections in health care workers have followed needle-stick injuries.<sup>11</sup> Risk of seroconversion to HIV-1 antibody-positivity after an injury with a needle contaminated with blood from an HIV-1-infected patient is less than 1 per cent.<sup>11, 24</sup>

Because our primary risk of HIV-1 infection is by needle-stick injury, we should avoid direct handling and recapping of contaminated needles. The use of puncture-resistant needle disposal units near the site of needle use, stopcocks in intravenous lines, and meticulous attention to needle handling will eliminate most risk of needle-stick injury. Injuries will, nevertheless, occur and recommendations for care are found in Table 4.<sup>10</sup> A double-blind, placebo-controlled trial is being conducted in the United States to evaluate the effectiveness of AZT given prophylactically to health care workers with needle-stick or mucosal exposure to HIV-1 infected blood.<sup>35</sup>

The Centers for Disease Control urges precautions be taken to avoid exposure to blood, semen, and vaginal secretions.<sup>14</sup> These body fluids contain lymphocytes and thus represent a risk for transmission of HIV-1. Other body fluids that are possible sources of HIV-1 include cerebrospinal, synovial, pleural, peritoneal, pericardial, and amniotic fluids. Precautions do not apply to many of the body fluids (other than blood) to which anesthesia personnel are routinely exposed. These

**Table 4.** *What If You Are Exposed to a Patient's Blood or Secretions?*

|                                                                                                                                                        |                                                                                                                                                                                             |
|--------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| The health care worker should report the incident to the appropriate medical department (that is, employee health service) who will initiate follow-up | If the patient refuses testing, or is HIV-1 seropositive, the health care worker should have an acute serum tested and should be followed at 6, 12, and 24 weeks with HIV antibody testing. |
| The patient should be asked for permission to test for HIV antibody, if any risk factors are present                                                   | If negative at 24 weeks, stop follow-up unless symptomatic                                                                                                                                  |
| The health care worker should be counseled about the exposure and be practical in treating the wound site                                              | Consider participation in AZT trial                                                                                                                                                         |

include sputum, saliva, nasal secretions, tears, urine, vomitus, and feces *unless* they contain visible blood. The use of gloves will prevent cutaneous exposure to most body fluids. Several simple hygienic practices that should be observed by anesthesia personnel are listed in Table 5.

Routine preoperative screening of all patients for HIV-1 has been advocated by some whereas most authorities feel this is unwarranted. Proponents of screening believe that preoperative testing will decrease the risk of HIV-1 transmission to medical personnel and improve patient care. There is no evidence to support a decrease in risk or improvement in care in surgical patients when HIV-1 status is known and "extraordinary vigilance" is taken to avoid body fluids or needle sticks. Opponents of routine screening suggest that extraordinary vigilance should be the normal care for all patients.<sup>34</sup>

Evaluation of the efficacy of routine screening is further complicated by the lack of complete sensitivity and specificity of serologic tests for HIV-1 antibodies. False-positive results will occur and, if results are not guarded for confidentiality, patients may suffer emotionally, socially, and financially.<sup>6, 25, 26, 33, 44</sup> To some degree, the efficacy of detecting patients who have HIV-1 infection by routine preoperative screening depends on the prevalence of HIV-1 infection in the community. Table 6 illustrates the positive and negative predictive value of combined ELISA and Western blot tests, using very good values of sensitivity (0.983) and specificity (0.994) in populations with different HIV-1 prevalences. For example, of 100 positive sam-

**Table 5.** *Protecting Ourselves*

|                                                                                                                                                          |
|----------------------------------------------------------------------------------------------------------------------------------------------------------|
| <i>All patients should be treated with good hygienic practices</i>                                                                                       |
| Consider all patients to be possibly infected                                                                                                            |
| Follow precautions when needles are used, use stopcocks when possible                                                                                    |
| Gloves should be worn if exposure to blood or secretions is anticipated                                                                                  |
| Eyewear should be used in situations in which blood or secretions may be spread                                                                          |
| Pregnant personnel are not at increased risk for HIV infections but should be alerted that HIV-infected patients are often infected with cytomegalovirus |

**Table 6.** *Positive and Negative Predictive Value of a Screening Test for HIV as a Function of Sensitivity, Specificity, and Prevalence*

| PREVALENCE | PREDICTIVE<br>VALUE (%)             |
|------------|-------------------------------------|
| 1/10,000   | Positive, 1.61<br>Negative, 100.00  |
| 1/1,000    | Positive, 14.09<br>Negative, 100.00 |
| 1/100      | Positive, 62.33<br>Negative, 99.98  |
| 1/10       | Positive, 94.79<br>Negative, 99.81  |

Sensitivity = 0.983; specificity = 0.994.

ples from persons in a community with a very low prevalence of HIV-1 infection of 1:10,000, two of these will be truly positive and 98 will be falsely positive. In contrast, of 100 positive samples from persons in a community with a very high prevalence of 1:10, 95 will be truly positive and five will be falsely positive. The greater the prevalence, the better the chance that a positive test result will be a true positive. If routine preoperative screening is to be done, it will be more accurate in communities with a high prevalence of HIV-1 infection.

### OTHER PATHOGENIC RETROVIRUSES

There are many subclassifications of retroviruses based on morphologic criteria.<sup>16</sup> At least six retroviruses have been found in humans in the past decade; of these, five are known to be pathogens.<sup>8, 55</sup> All five have been classified initially as human T-cell lymphotropic viruses (HTLV; the abbreviation HTLV is followed with a Roman numeral designating the order in which the virus was discovered). HTLVs are blood-borne viruses like HIV-1 (formerly HTLV-III) and are associated with immunodeficiency, neurologic disorders, and linked to the development of unique cancers. All are cytotrophic for T4 lymphocytes, monocytes, and macrophages.<sup>23</sup>

Subsequent study of the structure and pathogenicity of HTLVs has suggested the five pathogenic HTLVs be reclassified into two different groups.<sup>8</sup> The first consists of HTLV-I, HTLV-II, and HTLV-V. In 1978, HTLV-I became the first retrovirus identified in humans.<sup>46</sup> It causes a rare, highly malignant cancer called adult T-cell leukemia, found in parts of Japan, Africa, and the Caribbean. HTLV-II is linked, but not conclusively, to a T-cell variant of hairy cell leukemia and other chronic T-cell leukemias and lymphomas.<sup>23</sup> HTLV-V is a possible primary etiologic factor in cutaneous T-cell lymphomas, mycosis fungoides, and leukemias.<sup>40, 55</sup>

The second subgroup of HTLVs includes HTLV-III and HTLV-

IV,<sup>8</sup> which are distinct morphologically and genetically. Two independent groups of investigators isolated the virus responsible for AIDS at approximately the same time. One group called the virus HTLV-III whereas the other used the name LAV (lymphadenopathy-associated virus). Later, an international commission decided the virus should be called HIV-1 and changed HTLV-IV to HIV-2. HIV-2 is nearly identical to simian immunodeficiency virus (SIV; formerly simian T-cell lymphotropic virus or STLV), a retrovirus associated with malignant lymphoma in Old World monkeys, including macaques and African green monkeys.<sup>17</sup> This close association between HIV-2 and SIV suggests interspecies infection may have occurred between humans and monkeys. Humans with HIV-2 and green monkeys with SIV are found predominantly in Western Africa, although seroprevalence for both is increasing in Central Africa. The immunodeficiency caused by HIV-2 appears to be milder than that of HIV-1.<sup>17</sup> The reasons that HIV-2 infection does not progress as readily to AIDS as HIV-1 infection are not clear. HIV-2 may be less virulent or the progression to AIDS may take longer and, therefore, fewer patients have yet to develop HIV-2 related AIDS.

Thus far, the prevalence of infections with retroviruses other than HIV-1 is very low in North America. It is likely that other pathogenic retroviruses will be found.

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## Other Viral Infections

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The AIDS epidemic has renewed our awareness of the importance of viral infections and their control. However, it is well known that nosocomial infections, especially those caused by viruses, are an important source of morbidity and even mortality. This article surveys several viruses of particular relevance to anesthesia practice, whose importance has been overshadowed in recent years by the dual threats of AIDS and hepatitis. Necessarily, only the more salient features of these viruses are discussed here; for more information, the reader should consult several more detailed reviews.<sup>22, 60, 61</sup>

### HERPES SIMPLEX VIRUS

Herpes simplex virus (HSV) is actually a pair of viruses, themselves members of a family that includes varicella zoster virus (causative agent of chicken pox and shingles), Epstein-Barr virus (causative agent of infectious mononucleosis and a chronic fatigue disorder), and cytomegalovirus. HSV infections are among the most common and most varied affecting man. Anesthesia personnel may suffer a troublesome, painful, but self-limited finger infection, whereas their patients may experience recurrent skin infections and, under special circumstances, life-threatening visceral disease.

#### Epidemiology

HSV is ubiquitous and worldwide in its distribution. Curiously, although other animal species can be infected, man is the only known reservoir. The principal mode of transmission is direct contact with infected secretions: HSV type 1, which causes disease generally "above the belt," is spread primarily by oral secretions, and type 2 is spread by genital secretions. However, such anatomic distinctions are frequently violated.

The fetus and young infant are protected by transplacental ma-

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ternal antibody. Between 6 months and 5 years of age, infection with HSV is common, as indicated by acquisition of protective antibody. By age 15, as much as 96 per cent of the population possesses type-specific antibody, depending on socioeconomic conditions.<sup>6</sup> Whereas 80 to 100 per cent of adults in lower socioeconomic groups are immune, only 30 to 50 per cent of those in higher classes demonstrate seroconversion.<sup>48</sup>

### Clinical Features

Most initial infection is *subclinical*, making it impossible to determine susceptibility of an individual to HSV infection without antibody testing. Symptomatic infection, most common in young children, is characterized by nonspecific pharyngitis or gingivostomatitis, although ocular and skin sites may also be involved. Nonspecific constitutional symptoms may include fever, cervical adenopathy, and malaise. Virus is shed for months following infection, resulting in an unrecognized reservoir status.

Once the infection subsides, however, the virus remains in a *latent* state within sensory neurons innervating the site of what was the *primary infection*.<sup>2, 16, 63</sup> *Reactivation* of latent HSV infection is prompted by a wide variety of stimuli: fever, menstruation, corticosteroid or foreign protein administration, emotional stress, sunlight, and epidural morphine administration.<sup>7, 17, 30-32</sup> A surgical stimulus of particular note is surgery of the trigeminal nerve,<sup>9, 10, 24</sup> which pioneer neurosurgeon Cushing first described.<sup>18</sup> The resultant *recurrent infection* occurs in the vicinity of the primary infection—for example, herpes labialis (“cold sore” or “fever blister”) subsequent to gingivostomatitis—even in the presence of circulating antibody, but the symptomatology is generally milder than with the primary infection. However, in the presence of impaired immune mechanisms (malignancy, malnutrition, associated viral infections, thermal burns, defective cell-mediated immunity, drug-induced immune suppression, prematurity, and pregnancy) disseminated HSV infection can occur. Without vigorous supportive measures and specific antiviral chemotherapy, disseminated HSV infection is usually fatal. Figure 1 summarizes the possible courses that infection with HSV can take.

*Herpetic whitlow* is an HSV infection of the finger that is an occupational hazard of anesthesia practice.<sup>20, 50, 51</sup> This infection occurs when a minor finger injury, inapparent or overt, becomes contaminated with herpes-containing oral secretions. Whereas the herpetic finger infection experienced by children is associated with self-inoculation from concurrent gingivostomatitis or a parent “kissing the hurt,” the infection in adults occurs almost exclusively among health care workers who suffer trivial finger trauma and whose occupations expose them to oral secretions.

Stern et al<sup>59</sup> were the first to note this association among nurses, particularly those involved in oropharyngeal suctioning of postoperative neurosurgical patients. Typically, the nurses came from upper socioeconomic classes and lacked antibody to HSV. He termed the

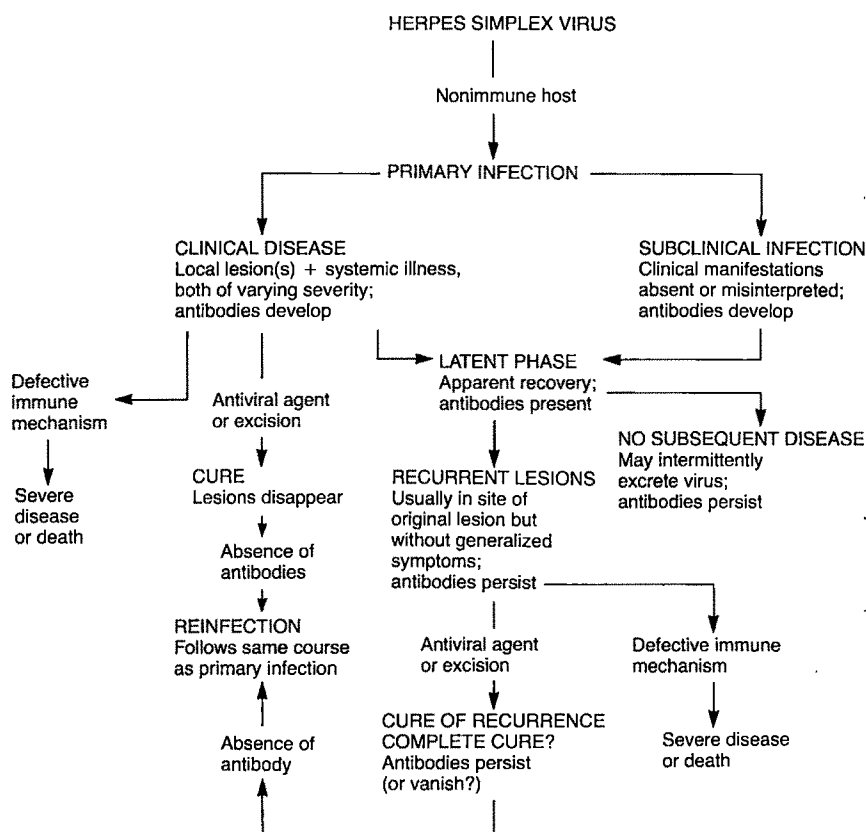


Figure 1. Schematic representation of the diverse clinical courses that HSV infection can take. (From Juel-Jensen BE, MacCallum FO: Herpes Simplex, Varicella and Zoster: Clinical Manifestations and Treatment. Philadelphia, Lippincott, 1972, p 32 as modified in Orkin FK: Herpetic whitlow. In Orkin FK, Cooperman LH (eds): Complications in Anesthesiology. Philadelphia, Lippincott, 1983, p 708; with permission.)

lesion a *whitlow* (synonym, felon) to emphasize its resemblance to pyogenic infection, such as the familiar paronychia. Usually conservative therapy without surgical drainage is appropriate. Secondary bacterial infection, often resistant to antibiotics, may occur. Although most individuals present with vesicles filled with clear fluid, permitting a clinical diagnosis, many have large bullous lesions that have formed from coalescence of vesicles. The affected digit typically becomes erythematous (then violaceous), edematous, and exquisitely tender.

Subsequent case reports have described this infection in surgeons, dentists, nurses, and anesthesiologists.<sup>20, 34, 50, 51, 55</sup> Fever, malaise, lymphangitis, and lymphadenopathy may accompany the infection, which usually results in a self-limited, although locally painful illness of about 3 weeks' duration.

Reactivation of HSV, usually involving the labia, by epidural morphine therapy has recently been described in postpartum obstetric patients.<sup>7, 17, 30-32</sup> Although nonobstetric patients receiving postoperative epidural morphine therapy rarely suffer recrudescence of HSV infection, about 15 per cent of postpartum patients do develop HSV labialis, for unknown reasons. This propensity to HSV recurrence may be related to a mild depression of cell-mediated immunity that occurs during pregnancy.<sup>32</sup>

### Anesthetic Implications

The ubiquity and infectivity of HSV, frequency with which minor finger trauma occurs, the uncertain immunity of anesthesia (and other health care) personnel, and morbidity and time lost to herpetic whitlow all argue for the importance of prevention. Fortunately, there are also some therapeutic options, as well.

Identify potential HSV carriers. In addition to those persons with obvious herpetic lesions, potential carriers include young children, recent convalescents from HSV infection, and a wide variety of patients with impaired immune defenses: malignancy (especially hematologic), malnutrition, other viral infection, defective cell-mediated immunity (for example, AIDS), thermal burns, and drug-induced immunosuppression. Similarly, anesthesia (and other) personnel with active and recent herpetic infections should refrain from treating patients with impaired host defenses.

Avoid unprotected contact with oral secretions of potential HSV carriers. The virus has been found in oral, oropharyngeal, and tracheobronchial secretions. The practice of wearing gloves adopted recently as protection against more severe infections (for example, hepatitis, AIDS) suffices.

Treat suspected herpetic whitlow lesions conservatively with immobilization, elevation, and analgesia. Especially tense, painful vesicles may be incised superficially to relieve discomfort; however, deep incision is contraindicated and may prolong the clinical course. Penicillin therapy is indicated, should lymphangitis appear.

Early treatment with specific antiviral agents *may* be beneficial in shortening the clinical course, if applied locally, for example, at the first appearance of a vesicle. Most of what is known about specific anti-HSV therapy has come from controlled clinical trials involving the more common and serious HSV infections, such as herpetic keratitis, meningoencephalitis, and neonatal and visceral herpetic infection. The extrapolation of chemotherapeutic experience from those infections to herpetic whitlow has resulted in anecdotal accounts, which often do not establish clinical efficacy. Nonetheless, judging from experience with herpetic labialis, acyclovir (9-[2-hydroxyethoxymethyl]-guanine, or acycloguanosine; Zovirax) is likely to be effective in aborting a recurrence, again, if applied to vesicles early as an ointment.<sup>33, 43, 58</sup> This drug is also available in oral and intravenous formulations. Although its use is associated with diminished viral shedding and shortened HSV infectivity, virus remains unaffected in

its latent state within sensory ganglia and can be reactivated with appropriate stimulation. A variety of other specific measures have been suggested, including other antiviral agents, interferon, physical agents, and limited surgery, but there is even greater uncertainty about their efficacy.<sup>51</sup>

## RUBELLA

German measles, or rubella, is a readily transmitted, typically benign, febrile illness. However, when it occurs during pregnancy, chronic infection of the fetus and congenital defects may result. Despite immunization programs and a substantial incidence of subclinical infection, many hospital personnel are susceptible to rubella infection. As a result, occasional outbreaks occur in hospitals, with cross infection of both personnel and patients.

### Epidemiology

Moderately contagious, rubella is transmitted via nasopharyngeal secretions, usually as droplets. Virus may be shed as early as 10 days before as well as about 2 weeks after the onset of clinical illness. However, perhaps half of rubella infections are subclinical and, thus, unrecognized. Before the introduction of a vaccine in 1969, epidemics occurred every 6 to 9 years, affecting millions of persons. In recent years, sporadic outbreaks have occurred, with only several hundred persons affected, mostly adolescents and young adults, who did not receive the benefit of immunization programs targeted to preschool children. Rubella infection, clinical or subclinical, results in immunity that is probably lifelong. Up to 15 per cent of hospital personnel are not immune to rubella and, thus, are at risk to not only contract the infection but also transmit it to others within the hospital.<sup>8, 11, 47, 53</sup>

### Clinical Features

Postnatal rubella is typically a very mild disease with nonspecific symptoms. Two to 3 weeks following exposure, a maculopapular rash appears on the face and spreads to the trunk and extremities. During the week preceding the appearance of the rash, adults often experience malaise, fever, headache, mild conjunctivitis, and lymphadenopathy.

Congenital rubella, in contrast, results in severe disease, which presents variously as congenital anomalies of a wide variety, premature birth, and fetal death.

### Anesthetic Implications

Like others working in the hospital, anesthesia personnel can unknowingly be vectors of rubella infection, especially in their contact with obstetric patients. The potential for nosocomial transmission and especially the severity of congenital rubella has prompted prevention programs aimed at hospital personnel.

Personnel screening for those lacking immunity by virtue of prior infection or for those who are unsure whether they received the vaccine is an important initial step in a prevention program. Some hospitals screen all new employees, including physicians.

Vaccination of nonimmune persons should be encouraged, if not required. Since the vaccine contains live rubella virus, the vaccination program should not include women who are pregnant, possibly pregnant, or likely to become pregnant in the following 3 months; patients with immune-deficiency diseases; and patients taking immunosuppressive drugs. Despite the mild effects of the vaccination for the larger healthy population and the potential seriousness of a hospital outbreak, compliance among physicians is typically poor.<sup>49, 53</sup>

Prevent virus transmission in an outbreak by restricting contact between patients, especially pregnant and prenatal patients, and those physicians, nurses, and other care givers identified as nonimmune. Susceptibles should be vaccinated as soon as possible.

## RESPIRATORY VIRUSES

A wide variety of respiratory viruses are easily transmitted and have been responsible for nosocomial outbreaks. Although anesthesia personnel have not been specifically cited as a risk group for either infection with or transmission of these viruses to patients, this specialty's intimate exposure to respiratory secretions gives special meaning to these viruses.

### Epidemiology and Salient Clinical Features

Common to the epidemiology of the respiratory viruses is transmission via small-particle aerosols (for example, coughing, sneezing) and close person-to-person contact.

Adenovirus is actually a group of some 30 serotypes that reside, often dormant for years, in the lymph glands surrounding the respiratory tract, as well as the gastrointestinal tract and conjunctiva. Children and military recruits are among those most commonly affected with acute respiratory illnesses characterized by fever, sore throat, cough, and sometimes conjunctivitis. Involvement of the conjunctiva raises the possibility that the virus may also be transmitted via contaminated ophthalmologic instruments or ointments.<sup>3, 19, 42</sup> Rather than having a seasonal predilection, adenovirus is endemic throughout the year.

Respiratory syncytial virus (RSV) is a member of the same family as viruses causing measles and mumps. However, this virus has gained notoriety for its involvement in outbreaks of infant pneumonia and bronchiolitis, especially nosocomial infections in newborn and pediatric intensive care units.<sup>36, 37, 57, 62, 65</sup> Lower nosocomial infection rates are associated with greater physical separation between children and with older age; attending nurses and physicians frequently become infected and ill.<sup>36</sup> The frail at the other age extreme are also at

risk for RSV pneumonia.<sup>46</sup> Although the virus is endemic in the community, illness rates are highest in the winter and early spring.

Influenza is among the best known respiratory viruses because of its propensity to cause sudden, rapidly spreading, community-wide epidemics that affect large numbers of patients and hospital personnel.<sup>52</sup> Within hospitals, the virus spreads rapidly in aerosols, in which it is especially stable. Severe illness claims the weakest patients, young and old, and is debilitating to the hospital staff, inflicting much absenteeism. Other staff may have subclinical infection and unknowingly transmit the virus to still other patients and staff. The cycle continues because a viral reservoir persists in the nasopharyngeal secretions of infected persons. The infection rate is highest in the winter and early spring.

Parainfluenza, an especially infectious agent, causes laryngotracheobronchitis (croup) and lower respiratory tract infection in children, but particularly infant pneumonia and bronchiolitis. This virus is endemic in the community, with no seasonal infection pattern.

Rhinovirus causes at least a third of the common colds. Although it can be transmitted by aerosols, this virus is much more likely to be transferred via contact with skin and environmental surfaces that have been contaminated by an infected aerosol and on which it is stable for long periods. Typically, the virus is acquired on one's hands and then transmitted to others by handshakes or to one's self by self-inoculation of the mucous membranes of the nose or eyes.<sup>35, 38</sup> Like parainfluenza and adenovirus, rhinovirus infection is endemic in the community rather than favoring a given time of year.

### Anesthetic Implications

The endemicity of these viruses, severe illness that they can cause, vulnerability of many hospitalized patients, and ease with which anesthesia and other hospital personnel can serve as vectors of transmission all argue for adhering to preventive recommendations that promote antisepsis.<sup>60</sup>

Wash hands frequently because this is the single most important initiative in preventing nosocomial infection due to any agent or organism. Hand contact with patients, equipment, and ourselves is so frequent throughout the typical work day that hands should be washed before and after each patient contact, as well as after any exposure to body fluids. Although iodophor and other disinfectant solutions are commonly available at hospital sinks, even washing with ordinary soap is sufficient in most situations. Since hands are colonized with virulent bacteria and washing does not reduce bacteria counts, disinfectant solutions should be used for hand washing before (and after) caring for immunosuppressed patients and infants.<sup>1, 56</sup>

Wear gloves in the anesthetic management of all patients to avoid contact with body fluids. Although this behavior has become more accepted during the AIDS epidemic, it has been recognized for some time as important in preventing the spread of respiratory viruses.<sup>44</sup> Gloves should be removed (or changed) after gross soilage and before

touching clean anesthesia equipment and ourselves. Paper masks should be used during contact with patients with known influenza, and gowns with all patients having respiratory virus infection. Goggles covering both the nose and eyes are effective in reducing the rate of RSV infection in hospital personnel caring for pediatric patients.<sup>28</sup>

Maintain good general infection control habits including keeping anesthetic equipment clean, avoiding contamination of work surfaces and equipment, and placing soiled apparatus in a container until it is cleaned. If ophthalmic lubricant is used, the ointment chosen should be a single-dose preparation. Apart from assuring that the breathing circuit is clean, no additional benefit accrues from the use of disposable tubing and filters.<sup>21, 25, 29</sup> However, as much disposable equipment as possible should be used in the care of patients with known respiratory infections. Nondisposable equipment that has been in contact with infectious oropharyngeal or other body fluids should be washed, then receive high level disinfection using an appropriate solution (sodium hypochlorite 1 per cent, activated glutaraldehyde 2 per cent, iodophors, or formaldehyde 10 per cent) or exposed to steam or ethylene oxide sterilization.

Immunization against influenza (annually) and rubella, as well as hepatitis B, is available and should be obtained if protective antibody titers are found to be insufficient. Amantadine may be useful, in preventing spread of influenza A to unvaccinated personnel during hospital outbreaks.

### CREUTZFELDT-JAKOB DISEASE

Creutzfeldt-Jakob disease (CJD) is a rare, but fatal, transmissible, subacute dementing brain disease whose natural mode of acquisition is unknown. Anesthesia and other surgical personnel risk infection during procedures in which instruments have become contaminated with transplant tissue or body fluids from an unrecognized infected individual.

#### Epidemiology

Although the precise mode of natural transmission is unknown, many clinical and histopathologic similarities between CJD and *kuru* (a chronic degenerative disease of the central nervous system, affecting primitive New Guinea tribesmen, known to be caused by a transmissible slow infection<sup>26, 40</sup>) have suggested similar transmission. The infectious agent is unusually small and of uncertain composition. It is highly cell membrane-associated, with *complete* destruction of the host cell membrane required to prevent infectivity. Thus, the agent is highly resistant to inactivation by many conventional physical and chemical means, such as formaldehyde, heat to 80°C, ultraviolet radiation, gamma radiation, and ultrasonic energy, and remains infective for years. Inactivation requires autoclaving (121°C, 20 lbs per inch<sup>2</sup>, 30 minutes), ethylene oxide sterilization, or exposure to hypochlorite

0.5 to 5.0 per cent, phenol 90 per cent, alcohol 70 per cent, or organic iodine disinfectant solutions, among others.

A decline in the prevalence rate of kuru has mirrored the decline in ritual cannibalism, suggesting that the infectious agent was transmitted through consumption of infected tissue, with an incubation period of up to 20 years. CJD occurs throughout the world, with a prevalence rate of about 1 per million. Geographical and temporal clusters of cases have been reported, especially among Libyan Jews whose dietary habits included eating sheep eyeballs,<sup>39</sup> with most cases occurring in the fifth to seventh decades of life. A case-control study in the United States found no relationship with occupation or exposure to others with the disease; however, among affected individuals there was a disproportionate dietary intake of hog brains.<sup>5</sup>

CJD has been transmitted to surgical patients by corneal transplant,<sup>23</sup> direct inoculation from contaminated stereotactic brain electrodes,<sup>4</sup> cadaveric dura mater graft,<sup>13, 14</sup> and presumed inoculation in a neurosurgical operating room in which a CJD patient had been treated weeks earlier.<sup>64</sup> In these iatrogenic cases, the incubation period ranged from 17 to 31 months. A case-control study of 60 affected patients noted that approximately three times as many of these individuals had surgery during the 5 years before disease onset as control patients.<sup>41</sup> The principal nonsurgical, iatrogenic mode of transmission has been therapy of growth retardation with human growth hormone derived from *pooled* cadaveric pituitary glands, which involved an estimated 10,000 children during the period 1963 to 1985.<sup>12</sup> Unlike many other viral infections, CJD is not transmitted through casual contact.

If one assumes a mid-range duration of infectivity of 10 years, there are potentially about 1400 infectious persons in the United States during any given year. Since about 8 per cent of the population undergoes surgery each year, about 100 infectious, but clinically well patients may be encountered in the operating room annually.<sup>54</sup> Given the substantial number of children who received pooled cadaveric human growth hormone, before it was replaced by synthetic hormone derived through recombinant DNA technology, there is probably a large, but unrecognized reservoir of infectious material.

Among 308 CJD patients studied in the principal series, only 18 were in health-related professions, including seven nurses, four dentists, two physicians, and one pediatric neurosurgeon.<sup>45</sup> No cases have been reported among anesthesia personnel.

### Clinical Features

Once symptomatology appear, CJD is a rapidly evolving neurodegenerative disease that begins with subtle behavioral changes and progresses through visual difficulties and mild mental deterioration to profound dementia, ataxia, diffuse myoclonic jerking, and finally stupor and coma. The entire disease progression typically occurs in less than a year. There is no cure. As noted, the patient is infectious well before clinical features appear and the diagnosis is made.

## Anesthetic Implications

CJD is a rare, potential threat to both the anesthesia provider and to subsequent patients who may be treated in the same setting. Given its epidemiology and clinical features, the focus must be prevention.

Identify potential carriers of the infectious agent. In addition to patients suffering from dementia (especially a rapidly progressive disease with myoclonus), all persons known to have received cadaveric human growth hormone or, perhaps, a neural tissue graft should be suspect. Isolation of CJD patients, however, appears unnecessary. These persons should not be considered as potential donors of blood, tissue, or organs.

Recognize the potential infectivity of *all* tissues and body fluids from suspected CJD carriers. Appropriate recommendations should be observed.<sup>15, 27</sup> Notify the hospital's infection control officer to make necessary arrangements with other hospital departments for handling of used equipment and other potentially infectious materials. Specimens sent to a laboratory should be marked "biohazard." Current practice recommendations regarding hand, eye, and mouth protection, advanced for protection against more prevalent infections (for example, hepatitis, AIDS) should suffice. Should unprotected contact occur, wash thoroughly with detergent. Accidental percutaneous exposure should be treated by cleansing the wound with a disinfectant solution that is appropriate for use on skin or other tissue.

Use appropriate decontamination and sterilization procedures for instruments and operating rooms in the care of *all* surgical patients.<sup>15, 17</sup> Thus, all potentially contaminated materials should be sterilized, preferably by autoclaving (121°C, 20 lbs per inch<sup>2</sup>, 30 minutes) or with an effective disinfectant solution. Strict adherence to recommended procedures is essential, because CJD's long latency makes surveillance of disease outbreaks ineffective as a control measure.

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## **Catheter-Related Sepsis**

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Infections resulting from the placement of various catheters into the vascular tree, as well as into the lower urinary tract, remain a major source of nosocomial morbidity in hospitals today. This review examines the currently available data regarding the diagnosis and management of these catheter-related infections. Emphasis will be placed on preventing such infections in the hope that patient care will be improved by the lowering of catheter-associated morbidity and that the hospital economics of using appropriate techniques and optimal equipment will also become more cost effective. Infections associated with the use of central venous, Swan-Ganz, intra-arterial, and urinary catheters will be examined.

### **CENTRAL VENOUS CATHETER SEPSIS**

The use of centrally placed venous catheters (CVC) for hemodynamic monitoring and for the infusion of fluids, blood products, drugs, or hyperalimentation has become one of the common therapeutic interventions of modern medicine. However, these intravenous catheters carry a significant potential for producing nosocomial sepsis. The incidence of septicemia due to CVCs ranges between 1 and 20 per cent, depending on the presence or absence of various factors that will be discussed later.<sup>41</sup>

The accepted definition of CVC-related sepsis differs between authors, and no single definition has been accepted. Most published studies incorporate one or more of the following definitions: (1) an episode of infection that clears within 24 hours after removal of the CVC; (2) clinical signs of sepsis associated with cultures of the catheter tip growing the same organism recovered from the peripheral

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blood; (3) a single positive blood culture obtained centrally or peripherally in a patient with clinical evidence of sepsis and no other source of infection.<sup>65</sup> Criteria for CVC sepsis are more specifically defined by the Association of Practitioners of Infection Control (APIC), as follows: (1) the patient exhibited symptoms of fever, leukocytosis, rigors, and/or chills; (2) blood or tip cultures were positive; (3) fevers resolved after the catheter was removed; and (4) patient exhibited no other sources of sepsis.<sup>60</sup>

The origin of most CVC-related sepsis is probably due to the introduction of bacteria into the catheter via two separate mechanisms. In the first, infections originate from organisms colonizing the skin at the insertion site leading to the inoculation of the catheter with subsequent propagation of the organism into the bloodstream, producing systemic sepsis.<sup>11, 41, 67</sup> More recent studies, however, indicate that contamination of the hub of the catheter with bacteria introduced during frequent catheter handling is a second mechanism. Bacteria migrate down the catheter lumen from the infected hub to the catheter tip, resulting in CVC sepsis.<sup>51, 66</sup> Based on these mechanisms of infection, it is not surprising that three types of skin-associated organisms predominate in CVC sepsis: coagulase-negative *Staphylococcus*, *Staphylococcus aureus*, and yeast.<sup>8</sup> Gram-negative rod bacteria, including *Enterobacter serratia*, *E. coli*, and *Klebsiella* play a smaller but significant role in CVC sepsis. These bacteria usually arise from pathologic processes within the pulmonary, gastrointestinal, or genitourinary tract and may secondarily infect the catheter by hematogenous dissemination.<sup>28, 36</sup> Additionally, gram-negative rod bacteria grow well in infusate solutions and, although infusate contamination is uncommon, this can lead to CVC sepsis. When this occurs, *Pseudomonas* or *Enterobacter* are the most common organisms cultured.<sup>41</sup>

Several factors have been identified that alter the risk of CVC-related sepsis. These have been reviewed by Hampton and Sherertz, and are listed as follows. Those factors that increase the risk of infection include an increased duration of catheterization, an increased number of catheter manipulations, an inexperienced inserter of the catheter, the use of transparent plastic dressings, the violation of aseptic technique, the use of multilumen catheters and, finally, the inadequate sterilization of reusable pressure transducers. Factors that decrease the risk of infection include the use of the team approach to catheter insertion, care, and maintenance, the use of chlorhexidine gluconate for skin preparation, the use of topical antibiotics, and the use of the subclavian vein approach for catheter insertion instead of the internal jugular or femoral veins.<sup>8</sup>

Currently, there are certain therapeutic considerations in the prevention of CVC sepsis that are controversial. The first controversy concerns the appropriate use of multilumen CVCs for simultaneous administration of parenteral nutrition along with drugs, fluids, and blood products. The second controversy deals with the indications, clinical utility, and complications of exchanging parenteral nutrition CVCs over guidewires. The third controversy is related to the second,

and concerns the prophylactic change or exchange of a CVC as an infection-control measure. Each of these controversies will be examined in the light of recent literature, and recommendations will be given accordingly.

### **Multilumen Versus Single-Lumen Central Venous Catheters**

Long-term central venous access in critically or chronically ill patients remains a very difficult problem. These patients often require the concurrent administration of medications and antibiotics, blood products, and total parenteral nutrition (TPN). In addition, frequent hemodynamic monitoring and blood sampling for laboratory tests are often necessary for optimum patient care, especially in the intensive care unit setting. Prior to 1980 with the advent of multilumen catheters (MLCs), multiple single-lumen catheters placed at various locations (subclavian, internal jugular, or femoral veins) were often necessary to accomplish the therapeutic and diagnostic functions necessary for the recovery of the patient. MLCs (double- and triple-lumen catheters) were developed to eliminate the need for multiple simultaneous single venous access catheters. However, a question that has arisen with their increased use is whether the increased availability and utilization of venous access through MLCs leads to a greater incidence of catheter contamination and resultant CVC sepsis. One would think so, especially if the hub theory of CVC sepsis applies. The literature with regard to this question, unfortunately, does not completely answer the question.

Several studies indicate that there is no increased rate of CVC sepsis with the use of MLCs. Miller et al<sup>54</sup> found the CVC sepsis incidence in MLCs to be only 7 per cent, which was consistent with the reported incidence seen in critically ill patients. This, however, was a short-term study, and all catheters were removed within 24 hours. Kaufmann<sup>34</sup> prospectively followed 104 MLCs in 74 critically ill patients. He found that the CVC sepsis rate in MLCs was 3.8 per cent compared with the 5.6 per cent infection rate found in SLCs of historical controls. Additionally, he noted that the use of TPN through the MLCs did not affect the CVC sepsis rate. Kelly et al<sup>35</sup> found a similar incidence of MLC-associated CVC sepsis (3.1 per cent) in 65 prospectively followed patients. These studies would lead one to believe that the use of the MLC is safe, well-tolerated, and cost-effective. One must be aware, however, that these were short-term studies with the average duration of the MLC being less than 10 days.<sup>60</sup>

Other studies support the incontrovertible axiom in nutritional support regarding the inviolate nature of the CVC that is being used for TPN. Rose et al<sup>62</sup> documented in 481 patients an increased sepsis rate in MLCs when compared with SLCs (4.6 versus 1.6 per cent). Pemberton et al,<sup>56</sup> in a prospective but nonrandomized study, found that the MLCs were associated with a CVC sepsis rate of 19 per cent as compared with 3 per cent in the SLC group. The MLC group was judged to be sicker however, and may therefore have been at greater risk for CVC sepsis. Wolfe et al,<sup>82</sup> in a prospective study conducted

from 1981 to 1985 in over 1600 patients receiving central venous TPN, documented an abrupt increase in the CVC sepsis rate from 2.1 per cent in 1981 to 10 per cent in 1985. Analysis of the rate of sepsis by catheter demonstrated that the SLC sepsis rate was unchanged, at 3.2 per cent. However, the frequency of the induction of catheter sepsis in the MLCs was 14.6 per cent, representing a fivefold increase. There were no data in this study to suggest that the increase was due to a change in patient population and therefore the 8 per cent increase in catheter sepsis rate from 1981 to 1985 was mostly due to infections from MLCs. Powell et al reported a 14 per cent CVC sepsis rate in MLCs as compared with a 7 per cent rate in SLCs. Finally, a prospective randomized trial by McCarthy et al<sup>51</sup> evaluating the use of SLCs and MLCs for TPN showed a higher CVC sepsis rate in the MLCs (12.8 to 0 per cent). These studies reiterate that MLCs are associated with an increased CVC sepsis rate when compared with SLCs, and therefore do not support the common clinical practice of using MLCs for the concomitant administration of TPN, drugs, blood products, and fluids as a matter of convenience. This is especially true if alternative venous access is available (that is, peripheral veins).

This leads to the question of what to do in the critically or chronically ill patient, when venous access is limited. Identification of an increased sepsis rate does not necessitate total abandonment of the use of MLCs with or without TPN. Further studies are required to compare overall patient morbidity when multiple SLCs are used with one being dedicated to TPN, or when an SLC is dedicated to TPN in addition to an MLC. Only one study has prospectively examined these conditions. Powell et al<sup>60</sup> compared the risk of a single MLC to bilateral subclavian SLCs in patients receiving TPN. Total infection rates in both groups were identical, although very high (22.7 per cent), which was attributed to a very critically ill patient population. Additionally, mechanical complication rates were much higher in the bilateral SLC group (22.7 versus 9 per cent). They concluded that a single MLC was superior in convenience and as safe as bilateral subclavian SLCs in high-risk individuals. Unfortunately, this study is marred by the fact that there is an inadequate description of the patient population in these two groups. Until further studies are done, the need for access to the central venous system via MLCs, especially when TPN is administered, must be judged in terms of potential risks and benefits, and individualized to the patient.

In light of the previous discussion, the following guidelines are offered for catheter selection: (1) SLCs are preferred for TPN, and should be used whenever possible. The need for additional intravenous access for the administration of blood products, fluids, and medications in the majority of hospitalized patients can be met with peripheral intravenous access. (2) MLCs for hyperalimentation and multiple drips may be used on a short-term basis primarily in patients in the intensive care unit who have peripheral venous access problems. (3) When an MLC is used, the middle port should be set aside to be used only for TPN and not be violated except under emergency

conditions. Should violation of the port occur, the catheter should be exchanged over a guidewire. (4) If the MLC has been used for pressure monitoring in the intensive care unit, the catheter should be replaced when the patient is transferred to the floor. (5) Swan-Ganz catheters should never be used for TPN except under extreme circumstances. A separate SLC should be placed for TPN if a Swan-Ganz catheter is already in place. (6) Consideration should be given to exchanging an MLC for an SLC for TPN if a patient is being transferred from the intensive care unit and if it is anticipated that TPN is going to be continued for more than a few days and the need for an MLC has decreased.

### **Guidewire Exchanges of Central Venous Catheters**

The use of guidewires to replace CVCs, including those used for hyperalimentation, has become routine in many institutions. The technique, which avoids a new needle venipuncture, involves placing a guidewire into the lumen of an existing CVC, removing the catheter, and threading the replacement catheter over the guidewire.<sup>16</sup> The technical advantages of guidewire catheter exchange are (1) it is more comfortable for the patient in that no venipuncture is necessary; (2) there is a decreased incidence of mechanical complications such as pneumothorax, arterial perforation, and hydrothorax; and (3) there is a decreased incidence of catheter malposition.<sup>81</sup> There appears to be no increased risk of CVC sepsis in catheters inserted by the guidewire technique if the discarded catheter is not infected.<sup>3, 57</sup>

The risks of guidewire catheter exchange include the following: (1) the potential for pulmonary embolism produced by dislodging intraluminal thrombi<sup>11</sup>; and (2) an increased risk of infection in the newly placed catheter if the old catheter was infected.<sup>3, 26, 57</sup> The exchange of a CVC over a guidewire in patients with septicemia is controversial. Graeve et al<sup>26</sup> noted that when a CVC catheter becomes colonized, the infection involves the whole length of the catheter, including the subcutaneous portion. When a new catheter is placed over a guidewire, it may be contaminated by the subcutaneous tunnel or by contact with a contaminated fibrin or thrombin sleeve, which enveloped the intravascular portion of the CVC. Alternatively, an infected thrombus may persist after removal of the old catheter and serve as a nidus for infection.

Bozzetti et al,<sup>11</sup> on the other hand, have recommended the use of weekly CVC guidewire exchanges not only in the diagnosis and prevention of CVC-related sepsis, but also in treatment, as well. To demonstrate this, 21 contaminated (culture positive) CVCs were exchanged weekly over a guidewire for a period of 4 weeks. Seventy-five per cent of the catheter cultures originally positive became negative after the first exchange. Virtually all catheter cultures were negative by the fourth exchange. Of greater interest was the fact that septic episodes resolved after the first exchange in all cases, even though the original catheter tips were culture positive.<sup>5</sup> In a follow-up study, Bozzetti et al noted that in 19 of 22 patients with positive blood cul-

tures, negative cultures were obtained after CVC exchange over a guidewire. Another Italian group reported similar results. Bonadimani et al<sup>7</sup> demonstrated resolution of sepsis in 15 of 17 cases (88 per cent) following guidewire exchange of CVCs that were culture positive with bacteria or fungus. Additionally, it is of interest that in one series, a majority of CVCs removed for suspected sepsis were found not to be the source of sepsis.<sup>57</sup>

Despite these results, our recommendations regarding CVC guidewire exchanges when sepsis is clinically suspected are based on the findings of Pettigrew and Greave, as well as our own clinical experience. If the suspicion for CVC-related sepsis is high and the patient is at low risk for percutaneous insertion of a new CVC, the old CVC is removed and cultured and a new CVC is inserted into an alternate site. If the suspicion of CVC-related sepsis is low or moderate or the patient is at high risk for insertion by new cannulation, the old CVC is exchanged over a guidewire for a new CVC, strictly adhering to aseptic technique. The suspect catheter is cultured and, if it yields significant growth, then the newly inserted catheter is promptly removed, followed by the insertion of a new CVC via a separate cannulation at an alternative site. This procedure allows for examination of the suspect CVC microbiologically and exclusion of the device as the source of infection without subjecting the patient to the risk of a new CVC insertion.<sup>41</sup>

Other indications for guidewire exchange of CVCs include mechanical malfunction of the catheter, fevers with unknown sources occurring without florid sepsis, patients at high risk for new insertions due to obesity, poor venous access or coagulopathy, and finally, suspected hyperalimentation catheter contamination without documented infection. A final indication for guidewire exchange may include the removal of a Swan-Ganz or MLC that has been in place for hemodynamic monitoring in order to place a new catheter and begin TPN. It should be remembered when performing guidewire catheter exchanges that strict aseptic technique should be used along with replacement of the entire delivery system including the administration set and fluid. As always, chest roentgenograms should be obtained to verify placement of the catheter into the superior vena cava just above the right atrium. Finally, all catheter tips should be cultured after removal whether or not sepsis is suspected.

### **Prophylactic Exchange of Central Venous Catheters**

The prophylactic exchange of a noninfected CVC over a guidewire or the removal of a CVC with placement of a new catheter at a separate site have been suggested as routine infection control measures. These practices are based on two studies that report a reduced sepsis rate when CVCs are prophylactically removed and replaced by these techniques. Bozzetti et al<sup>11</sup> noted that the CVC sepsis rate was reduced from 11.9 to 0 per cent when prophylactic exchange was performed on a weekly basis during the first month. After this period of time, CVC sepsis rate was not influenced by this prophylactic tech-

nique. These data should be interpreted cautiously, however, because historical controls were used for comparison and bacteriologic procedures were employed that do not reliably distinguish between insignificant catheter contamination and true CVC-related infection.<sup>81</sup> Mantese et al<sup>50</sup> compared two groups of patients who underwent prophylactic exchange or rotation to a new site of a previously placed MLC at 48 to 72 hours or at 73 to 120 hours. Although no significant differences in colonization or sepsis rates were noted between the two groups, the authors concluded that because early colonization of MLCs occurs frequently, prophylactic line changes may reduce the incidence of clinical CVC sepsis.

Powell et al,<sup>60</sup> on the other hand, found that frequent (every 3 days) prophylactic guidewire changes did not alter the incidence of CVC-related sepsis in patients with MLCs on TPN when compared with controls. Maki has concluded from his personal experience that there is no rationale for the practice of periodically and routinely replacing CVCs by guidewire exchange solely as a putative infection control measure. Additionally, the extensive manipulation inherent in insertion of a new catheter into the same tract by guidewire may well increase the risk of infection. In light of this discussion, routine guidewire changes as an infection control method are not generally recommended. However, every 3 to 4 days, routine guidewire changes may be performed in the following situations: (1) MLCs in patients with severe immunosuppression; (2) MLCs in patients with ongoing bacteremia and fungemia documented from other sources; (3) MLCs in patients who would not tolerate complications of a septic episode; and (4) SLCs or MLCs in patients who undergo procedures that may cause seeding of the catheter with bacteria or fungi, such as genitourinary procedures, abscess drainage, or wound debridements. These specific exceptions are based on the author's clinical experience only.

## FLOW-DIRECTED PULMONARY ARTERY CATHETERS

Flow-directed, balloon tip pulmonary artery catheters (PAC) have been used to assess fluid therapy and monitor cardiac hemodynamics in postsurgical patients with shock or cardiorespiratory failure. Catheter-induced sepsis from these catheters has been reported to be as high as 10 per cent.<sup>54</sup> This probably reflects contamination from the frequent handling that occurs during their use. Applefield reported that patients with PACs in place longer than 72 hours or those catheters that had been positioned more than three times were more likely to yield positive blood cultures drawn through the catheter.<sup>1</sup> It has therefore been recommended that these catheters should be replaced every third day in patients who require them for prolonged periods. PACs should not be used for TPN except under extreme circumstances.

## ATTACHABLE SILVER IMPREGNATED CUFF

Maki et al<sup>48</sup> have described the use of an attachable silver impregnated cuff (VitaCuff) that serves as a tissue interface barrier against invasion by extrinsic organisms from the skin. A threefold reduction in catheter-related infection has been described. Flowers et al,<sup>18</sup> in a more recent trial, confirm the efficacy of this device in reducing CVC-related sepsis, from 13.8 per cent in controls to 0 per cent for cuffed catheters.

## URINARY CATHETER-RELATED INFECTIONS

Urinary catheter-induced infections are the most frequent and intractable problem in hospital infection control. Approximately 35 to 40 per cent of nosocomial infections are related to the urinary tract and these may be associated with fatal gram-negative sepsis.<sup>26</sup> With the exception of urethritis and trauma, virtually all complications of urinary catheterization are the result of consequent bacteriuria.<sup>19, 73</sup> The catheter is a major factor in the development and maintenance of bacteriuria, not only allowing the ingress of micro-organisms to the bladder, but also providing a niche for bacteria on its luminal and external surfaces.<sup>13, 22, 39, 40</sup> The catheter may also impair polymorphonuclear leukocyte function by producing mechanically or chemically induced inflammation of the urethra and bladder lining.<sup>83, 84</sup>

The four main indications for indwelling catheterization of the bladder are for surgical procedures, urinary incontinence, urine output measurement, and treatment of urinary retention. Most patients in acute care hospitals have indwelling urinary catheters for only short periods of time, usually 2 to 4 days.<sup>23, 29</sup> However, between 10 and 30 per cent of these short-term catheterized patients develop bacteriuria. Table 1 illustrates the characteristics of patients who require short-term catheterization and resultant outcome.

The most important advance in catheter technology was the introduction of the "closed-catheter" drainage system 20 to 30 years ago.<sup>15, 38</sup> A "closed" collecting system is one in which the drainage

Table 1. *Characteristics of Short-Term Urinary Catheterization*

|                          |                         |
|--------------------------|-------------------------|
| Definition               | <30 days                |
| Usual duration           | 2-4 days                |
| Incidence of bacteriuria | 5-10%/day               |
| Prevalence               | 15%                     |
| Type of patient          | Acutely ill/in hospital |
| Complications            | Fevers                  |
|                          | Acute pyelonephritis    |
|                          | Bacteremia              |
|                          | Death                   |

**Table 2.** *Evolution of Improved Urinary Catheter Care*

| YEAR | OBSERVATION                                                                                                  |
|------|--------------------------------------------------------------------------------------------------------------|
| 1928 | Dukes establishes the value of a closed drainage system in preventing urinary tract infections <sup>38</sup> |
| 1954 | The development of sterile intermittent catheterization <sup>63</sup>                                        |
| 1957 | Demonstration of the importance of the periurethral route of bacterial entrance <sup>64</sup>                |
| 1960 | Aseptic management of the catheter system <sup>65</sup>                                                      |
| 1966 | Establishment of the value of plastic drainage bags in preventing infection <sup>66</sup>                    |
| 1973 | Demonstration that cross-infection may occur among patients <sup>67</sup>                                    |

tube empties directly into a receptacle so that the urine is always contained within a lumen and protected from environmental contamination. Prior to this innovation, the catheter consisted of an indwelling bladder tube that emptied into an open bottle. Sixty to 100 per cent of patients who were catheterized in this manner developed bacteriuria within 4 days of catheterization. Table 2 traces the understanding of catheter-related infections and the means of prevention.

### Risk Factors

Platt et al<sup>59</sup> used multivariant analysis to determine the following risk factors associated with bacteriuria: (1) duration of catheterization; (2) absence of antibiotic use; (3) microbial colonization of the drainage bag; (4) women patients; and (5) diabetes mellitus. Garibaldi et al, as well as others, demonstrated periurethral colonization with potential uropathogens as another important risk factor in the development of bacteriuria.<sup>13, 23, 64</sup>

External organisms may enter the catheterized urinary tract, either through the lumen or along the external surface of the catheter. As long as the initially sterile catheter system remains closed, micro-organisms are unable to reach the bladder through the lumen of the catheter. The "closed" catheter system may, however, be opened at two points. The first is the drainage tube on the drainage bag, which is opened periodically to empty urine from the bag.<sup>23</sup> If, at this time, the lumen of the drainage tube becomes contaminated, the bacteria are capable of multiplying to high concentrations and entering the drainage bag. A large number of micro-organisms along the internal surface of the bag facilitates their ascent to the lumen of the catheter.<sup>40</sup> Second, the junction between the catheter and the collection tube offers another site of entry into the lumen of the catheter. Warren et al<sup>78</sup> demonstrated a higher incidence of bacteriuria on days when catheter-collection tube disconnections occur.

Bacteria may enter the catheterized urinary tract even when the closed system remains intact. The primary site of entry is the urethra itself. Bacteria colonizing the periurethral area appear to migrate into the bladder through the space between the catheter surface and the

urethral mucosa. Numerous studies show that bacteria isolated from the urethral meatus just prior to catheterization are identifiable several days later in bladder urine.<sup>8, 13</sup> Burke et al<sup>12</sup> demonstrated that the mucous sheath between the catheter and urethra is the major pathway for bacterial entry into the bladder when a closed drainage system is used.<sup>12</sup>

### Diagnosis

The diagnosis of catheter-related bacteriuria has been established by many studies as the presence of at least 100,000 colony-forming units (cfu) per mL of urine aspirated from the distal catheter. Stark et al indicated that the majority of organisms initially present in catheter urine at concentrations less than 100 cfu per mL have the capability of reaching concentrations of at least 100,000 cfu per mL over succeeding days.<sup>71</sup> This study suggests that organisms present in small numbers in the urine during short-term catheterization may represent bacterial residence rather than contamination. Stamm et al<sup>70</sup> suggested that a diagnosis of infection requires evidence of tissue injury or invasion, and demonstrated pyuria in catheter-associated bacteriuria patients, thereby implying a host response to infection rather than colonization.

*Escherichia coli* is the commonest species isolated in patients catheterized for a short period of time. Other micro-organisms include *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Staphylococcus epidermidis*, and *Enterococcus*. Table 3 lists the incidence of common organisms associated with short-term catheterization-related bacteriuria. When patients are receiving antibiotics, yeast may also be isolated in catheterized urine.

### Prevention

Guidelines aimed at preventing bacteriuria associated with short-term catheterization may be divided into two groups: avoidance of urethral catheterization and prevention of bacteriuria. The most direct

Table 3. Incidence of Selected Organisms Isolation from Short-Term Catheterized Bacteriuria

| ORGANISM                         | PER CENT<br>INCIDENCE |
|----------------------------------|-----------------------|
| <i>Proteus</i> species           | 6                     |
| <i>Escherichia coli</i>          | 24                    |
| <i>Pseudomonas aeruginosa</i>    | 9                     |
| <i>Enterococcus</i>              | 7                     |
| <i>Klebsiella</i> species        | 8                     |
| Coagulase-negative Staphylococci | 8                     |
| Yeast                            | 26                    |

Adapted from Ladd TI, Schmiel D, Nickel JC, et al: Rapid method for detection of adherent bacteria on Foley urinary catheters. J Clin Microbiol 21:1004-1006, 1985.

method to prevent catheter-related bacteriuria is to avoid catheterization. However, in the patient who requires catheterization, one should weigh the risks and benefits, determine the appropriate indications for short-term catheter use, and evaluate alternatives to urethral catheterization.

Suprapubic catheterization has been used in gynecologic, urologic, and pelvic or abdominal operations, and offers an alternative to urethral catheterization. Many studies demonstrate the rate of bacteriuria to be lower with suprapubic catheters than with urethral catheters; however, not all studies have had satisfactory designs.<sup>20, 31, 32</sup> In a well-designed study by Andersen et al,<sup>2</sup> it was demonstrated that patients with indwelling urethral catheters for 5 days had a significantly higher rate of bacteriuria than patients in the suprapubic catheter group. Reported complications of suprapubic catheterization include cellulitis, leakage, and hematoma at the insertion site.

Another alternative to short-term indwelling urethral catheterization is intermittent catheterization. In patients who are unable to void postoperatively, intermittent in-and-out catheterization may be sufficient to drain the bladder until the patient is able to void normally. The instillation of povidone iodine before removal of the catheter was demonstrated by Van Den Broek et al<sup>76</sup> to reduce the rate of bacteriuria.

The single most important preventive measure, once an indwelling catheter is in place, is to remove it. The evolution of the closed catheter system simply allowed postponement of bacteriuria; if the catheter is removed before bacteriuria develops, the postponement becomes prevention. To further postpone bacteriuria, several modifications to the closed system have been attempted to prevent bacterial entry and to inhibit bacterial growth.

Because disconnection of the junction between the catheter and the collecting tube increases the risk of bacteriuria, urine specimens should be obtained without violating this junction. Specimens may be obtained by puncturing the port on the catheter designed for specimen collection with a small-gauge needle and syringe.<sup>37</sup> Another point of entry for bacteria is made accessible when the drainage bag is opened. Medical personnel should carefully drain urine from the collection bag to avoid contaminating the distal end of the drainage tube. When the catheter system remains closed, the only other point of bacterial entry is the urethra; in particular, the space between the catheter and the urethral mucosa.<sup>3, 13</sup> To prevent this from occurring, some advocate periodically washing the periurethral area with antimicrobial soap.<sup>53, 79</sup> However, Burke et al<sup>12</sup> have reported several controlled trials which indicate little justification for this practice.

Measures to inhibit or kill bacteria after entry have primarily been aimed at the collection bag, irrigation of the bladder, and the use of systemic antibiotics. Various methods have been attempted to limit bacterial growth by instilling antibacterial substances such as formaldehyde, hydrogen peroxide, and chlorhexidine directly into the collection bag.<sup>25, 68, 74</sup> Most well-designed studies have failed to dem-

onstrate a reduction in the incidence of bacteriuria in patients treated in this way.<sup>24, 72, 74</sup> Other attempts to control bacterial growth include continuous or intermittent irrigation of the catheter with antibacterial solutions. Continuous irrigation usually requires an extra catheter lumen and, unless the catheter is periodically clamped, the irrigation solution bathes only a small portion of the bladder.<sup>30, 85</sup> Continuous irrigation using various solutions (chlorhexidine, neomycin, and neomycin-polymyxin) in controlled trials have failed to demonstrate any benefit in postponing bacteriuria.<sup>5, 40, 63</sup> The use of intermittent bladder irrigation requires frequent interruptions of the closed catheter system and there are, to date, no properly designed prospective studies evaluating the efficacy of this method in postponing bacteriuria.

The use of systemic antibiotics is the only medical treatment that has shown effectiveness in postponing catheter-related bacteriuria. Patients receiving antibiotics have a lower incidence of bacteriuria than those who do not receive antibiotics.<sup>22</sup> In general, antibiotics only postpone rather than prevent the onset of bacteriuria, and only patients who are catheterized for short periods of time are protected from bacteriuria with the use of antibiotics.<sup>59</sup> If bacteriuria does occur in catheterized patients who are receiving antibiotics, the organisms may be resistant to the antibiotics used.

### Treatment

In some patients, the bacteriuria associated with indwelling urinary catheters will spontaneously resolve once the catheter is removed.<sup>2, 29</sup> Approximately 50 per cent of these bacteriurias are asymptomatic and only half these patients require treatment. An exception to this is the asymptomatic bacteriuria caused by a urease-producing organism such as *Proteus*. With these organisms, the possibility of rapidly forming renal stones mandates antibiotic therapy. Upon removal of the catheter, a culture of the catheterized urine is recommended. If organisms are found in any concentrations, a repeat culture should be obtained in a week. Most patients will have cleared the bacteria by this time; however, those who do not may require oral antibiotic therapy.

It is reasonable to treat symptomatic patients with systemic antibiotics. Symptomatic infections may range from mild lower urinary tract conditions without fever, such as cystitis, to toxic febrile conditions, such as acute pyelonephritis, bacteremia and shock, and death. In the patient who develops fever or signs of bacteremia, it is important to rule out catheter obstruction and periurethral infection. Initially, urine and blood samples are obtained for culture and sensitivity testing. After this, parenteral antibiotics are administered at doses high enough to achieve adequate serum levels to combat possible bacteremia. Empirically, a combination of an aminoglycoside plus ampicillin or an extended-spectrum penicillin may be initiated and then, based on culture and sensitivity results, the regimen may be adjusted.

## ARTERIAL CATHETER-RELATED INFECTIONS

Indwelling arterial catheters are widely used for continuous monitoring of systemic blood pressure and obtaining blood for oxygen, carbon dioxide, and pH analysis.<sup>17, 55, 58</sup> Arterial catheterization permits multiple blood samplings and is less painful than repeated arterial punctures. Arterial punctures and catheterization are not benign procedures. Complications include thrombus formation, arterial occlusion with distal ischemia, aneurysm formation; infection, sensory loss distal to the catheter, and hematoma formation.

Infusion-related sepsis is probably the most insidious and least frequently recognized nosocomial infection.<sup>42, 47</sup> It is estimated that over 80,000 patients are monitored yearly with arterial catheters. Although valuable information is derived from arterial monitoring, the potential for infection is considerable, and the frequency has not been defined. Several studies have shown that the fluid within the monitoring system can become contaminated by gram-negative bacilli, which may result in bacteremia<sup>77, 80</sup>; however, the infectious risks due to the arterial catheter itself have not been well characterized. In 1970, Michaelson and Walsh<sup>52</sup> published the first report of septicemia originating from an arterial catheter. Eight other prospective studies identified only two bacteremias secondary to arterial catheterization; however, catheters were not routinely cultured in most of these studies.<sup>6, 9, 16</sup>

Bacteremia may result from contaminated heparinized saline flush solution,<sup>77</sup> nondisposable pressure transducer domes,<sup>80</sup> and from ice used to cool heparinized syringes used for sampling.<sup>69</sup> Gardner et al<sup>21</sup> initially examined the risk of infection associated with arterial catheters by culturing 200 radial artery catheters and found eight cultures positive. Others did not prospectively evaluate catheter-related infections.<sup>9, 16</sup> Band and Maki<sup>4</sup> pointed out that arterial catheters used for hemodynamic monitoring pose a significant risk of infection and must receive stringent aseptic care. They demonstrated a 12 per cent incidence of bacteremias in their study population.

### Risk Factors

Band and Maki<sup>4</sup> determined several factors that strongly correlate with an increased risk of infection from arterial catheters. These include local inflammation, catheter placement by surgical cutdown, and catheter placements exceeding 4 days.

Although the factors contributing to catheter-related inflammation are still unclear, there appears to be a causal relationship between inflammation and associated infections of catheter wounds and bacteremic infections.<sup>21, 45, 69</sup> However, the absence of inflammation should not be used to exclude catheter-related infections.

Several uncontrolled studies examining venous catheters that were placed by surgical cutdown demonstrated a higher incidence of catheter-related sepsis.<sup>6</sup> Arterial catheters may be placed by cutdown when percutaneous attempts are unsuccessful. Maki et al<sup>46</sup> demon-

strated an increased risk of catheter-related bacteremia in patients who had difficult arterial cannulation or whose catheters later required manipulation. Because of this risk factor, the percutaneous placement of arterial catheters is preferred to insertion by cutdown.

Multiple studies have suggested an increased risk of bacteremic infections with peripheral venous catheters after 48 to 72 hours of placement.<sup>43</sup> However, there is little comparable data in the literature to guide the management of arterial catheters. Prospective studies have suggested that arterial catheters may be left in place at relatively low risk for up to 4 days.<sup>4</sup>

### Microbiology

In contrast to the microbiologic profile of infections caused by venous catheters, *Candida*, enterococci, and gram-negative bacilli have been isolated in arterial catheter-related infections. This difference in the microbiology profile may have several causes. Most patients having prolonged arterial catheters in place are critically ill and will receive broad spectrum antibiotics. The administration of broad spectrum antibiotics produces a change in bacterial flora. Alternatively, the bacteria may be introduced from the environment of the critical care unit.

### Diagnosis and Treatment

The clinical features of arterial catheter-related infections are not distinguishable from those of venous catheter-related infections. Patients may exhibit Osler's nodes distal to the catheter as demonstrated by other authors reporting septic endarteritis.<sup>16a, 52</sup> Removal of the catheter is the most important step in management of catheter-related infections including those related to arterial catheters. Often antibiotics are ineffective until the implicated catheter is totally discontinued.<sup>43, 47</sup> The application of topical antibiotic ointment to the catheter may confer some protection against infection; however, the micro-

Table 4. Guidelines for Care of Arterial Catheters

- 
1. Wear sterile gloves when inserting arterial catheter
  2. Disinfect the site with an iodine containing antiseptic or an iodophor ointment and use sterile drapes
  3. Make every effort to use the percutaneous approach to inserting the catheter and avoid surgical cutdown if possible
  4. Anchor the catheter securely
  5. Apply iodophor ointment to the insertion site and place sterile occlusive dressing over site
  6. Record time and date of insertion. Arterial catheters should not be left in place for longer than 4 days
  7. Dressings are changed every 72 hours and as needed if the dressing becomes non-occlusive or moist. Iodophor ointment may be reapplied
  8. The condition of the insertion site, presence or absence of redness, swelling, heat or tenderness is assessed every 24 hours. Any purulence that can be expressed from the site should be gram-stained and cultured
-

biologic pathogens that predominate in arterial catheters are frequently resistant to the drugs contained in these products.<sup>69</sup> If a topical agent is to be used, an iodophor ointment may be preferred.

### Prevention

Recommended guidelines for the cleansing and sterilization of pressure monitoring systems and for the care of infusion apparatus have been published by several authors.<sup>46, 61</sup> Recommendations for the care of arterial catheters are summarized in Table 4.

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## Bacterial Septic Shock

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Bacterial sepsis and shock are common clinical problems with high morbidity and mortality. During the last 8 years, we have conducted clinical and laboratory studies in the medical intensive care unit (ICU) at the National Institutes of Health (NIH) to characterize better the pathophysiology of the cardiovascular abnormality associated with septic shock. In addition, we have developed a canine model of septic shock that simulates the hemodynamic abnormalities of human septic shock. Using this model, we have been able to evaluate microbiology, physiology, and therapy in controlled experiments. Data from these and other studies have provided important insights into the pathophysiology and therapy of this highly lethal disorder.

### PREVALENCE OF BACTERIAL SHOCK

Septic shock, a syndrome caused by either bacteria or fungi (and possibly parasites and viruses), is now the most frequent cause of death in ICUs in the United States.<sup>41, 59</sup> Death from septic shock in the first few days from onset of illness is frequently caused by refractory hypotension with a low systemic vascular resistance (SVR). In the later stages of the disease, the most frequent cause of death is sepsis-induced multiple organ system failure syndrome (pulmonary failure from ARDS, renal insufficiency, hepatic insufficiency, bone marrow failure, CNS dysfunction, and so forth).<sup>41</sup> Despite effective antibiotic therapy, bacterial shock remains the most prevalent clinical problem in ICUs, and, unfortunately, causes high mortality.

Over the last 50 years, the incidence of bacterial sepsis has stead-

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ily increased. This increase has been caused, in part, by the expanded therapeutic use of potent cytotoxic and immunosuppressive drugs that cause neutropenia or other significant dysfunction of the immune system. In addition, increased use of life support systems (for example, ventilators, dialysis, cardiopulmonary bypass) has resulted in a large hospital-based population at risk for nosocomial infection. Paradoxically, the increased use of broad-spectrum antibiotics has not decreased the incidence of infection but has instead increased the prevalence of infections caused by resistant micro-organisms, which are often difficult to eradicate. In the 1970s, the incidence of gram-negative bacteremia was estimated at 300,000 cases and 100,000 deaths per year. These figures are probably significantly below those of more recent years.<sup>13, 23</sup> Thus, major clinical advances in chemotherapy, antimicrobial therapy, and supportive care over the past few decades have contributed to the difficult problem of bacterial sepsis in the ICU.

## DIAGNOSIS

Patients with sepsis or septic shock have a variety of diverse symptoms: fever, malaise, hypotension, cool extremities with a warm trunk, and chills or rigors. In addition, these patients often have clinical signs that indicate the source of infection. For example, a stiff neck and mental status changes suggest meningitis; productive cough, chest pain, shortness of breath indicate pneumonia or pleural empyema; abdominal pain with guarding suggests peritonitis; and, flank pain and dysuria indicate pyelonephritis. However, many patients (especially those who are elderly or immunocompromised) do not have the typical symptoms and signs associated with sepsis. Therefore, shock caused by sepsis is often difficult to diagnose. Because the disease is so rapidly lethal (40 to 90 per cent mortality), clinicians should suspect the possibility of septic shock early and treat the disease well before complete diagnostic and clinical information is available.<sup>23, 33, 36, 41, 60</sup>

Of all patients who have symptoms that suggest diagnosis of septic shock, only about 50 per cent have a positive blood culture.<sup>23, 41</sup> In our experience obtaining more than three blood cultures serially does not increase the percentage of patients having a positive culture. Patients on antibiotics are less likely than patients not on antibiotics to have positive cultures. Forty per cent of patients with positive blood cultures will develop septic shock hemodynamics (hypotension, high cardiac output [CO], low SVR).<sup>23, 36, 41, 60</sup>

It is not known why half of patients with clinical septic shock do not have a documented bacteremia. In some cases, negative cultures may result from sampling errors, such as false negative findings that result from intermittent bacteremia or concurrent antimicrobial therapy. In other cases, bacterial toxins may be released into the bloodstream without bacteria from the source of infection. Nonetheless, it

is important to note that a negative blood culture does not exclude the diagnosis of septic shock.

### CARDIOVASCULAR ABNORMALITY IN HUMAN SEPTIC SHOCK

Prior to the mid-1960s, septic shock was thought to be associated with a decreased CO.<sup>56, 57</sup> In 1965, however, it was reported that humans with septic shock had normal or increased CO and low SVR levels.<sup>59</sup> This finding was confirmed in many subsequent studies, and thus septic shock was firmly demonstrated to be a form of distributive shock. Furthermore, the finding that patients in septic shock had increased or normal CO cast doubt on the hypothesis that myocardial depression was caused by this syndrome.<sup>21, 59</sup>

During the 1960s, understanding of the hemodynamic abnormality of severe sepsis changed significantly, probably because of changes in patient management. During this period, clinicians began to monitor central venous pressure (CVP) and pulmonary capillary wedge pressure (PCWP). Fluid administration was titrated to these pressures and large volumes were given to patients. With adequate preload, investigators found that patients with septic shock had increased or normal CO. Thus, it is likely that earlier studies of septic shock found a low CO because preload was insufficient.

In recent studies at the NIH, serial hemodynamics of septic shock patients have been evaluated. Using radionuclide gated blood pool scans simultaneously with pulmonary artery catheter pressures and thermodilution CO measurements, serial measurements of systemic pressures, flows, and left ventricular (LV) volumes could be measured during septic shock.<sup>32, 37, 38</sup> These investigations demonstrate (Fig. 1A) that patients with septic shock develop a significant decrease in LV ejection fraction (EF) within 24 hours of the onset of hypotension. The decrease in EF is associated with LV dilation and maintenance of stroke volume (SV) and CO. In survivors, these abnormalities return to normal by 7 to 10 days. Radionuclide studies of right ventricular (RV) EF also show decreased RVEF and RV dilation. Thus, serial evaluations employing radionuclide heart scans reveal RV and LV dysfunction during sepsis that is not evident with evaluation of CO alone.

In studies at NIH, Frank-Starling plots confirmed the existence of myocardial depression in septic shock. Patients with septic shock had smaller increases in LV stroke work (LVSW) per increase in LV end-diastolic volume (EDV) (produced by volume infusion) than other critically ill patients not in septic shock (Fig. 2A).<sup>32</sup> In addition, when LVSW versus EDV for septic shock patients was plotted, the curve was downward and to the right, confirming the primary LV dysfunction of sepsis.

When survivors of septic shock are compared with nonsurvivors, they have different cardiovascular changes. Although both survivors

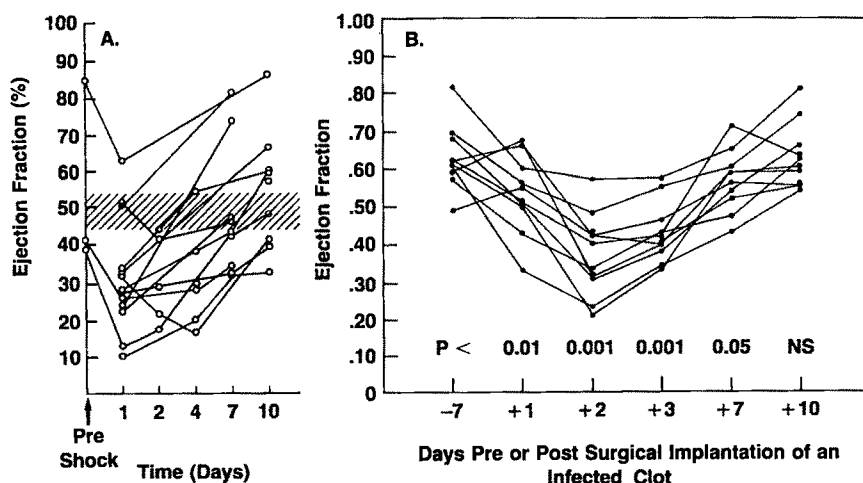


Figure 1. Serial LVEFs versus time of (A) humans with septic shock, and (B) the canine model of septic shock. Individual patient or dog EFs are indicated by circles, and the lines connect days. The hatched area in A is the normal range. In both A and B, the LVEF profoundly decreases at 2 to 4 days and recovers in 7 to 10 days. (Modified from Parker MM, McCarty KE, Ognibene FP, et al: Similar patterns of left and right ventricular dysfunction in survivors and nonsurvivors of septic shock in humans. *Ann Intern Med* 100:483-490, 1984; and Natanson C, Fink MP, Ballantyne HK, et al: Gram-negative bacteremia produces both severe systolic and diastolic cardiac dysfunction in a canine model that simulates human septic shock. *J Clin Invest* 78:259, 1986; with permission.)

and nonsurvivors have increased CO and heart rate (HR), decreased SVR, and normal stroke volume (SV) during the initial phases of sepsis, survivors are more likely than nonsurvivors to have a decreased LVEF with LV dilation.<sup>37</sup> Although the reasons for this are unknown, LV dilation provides compensation (when LVEF is decreased) to maintain SV and CO (by the Frank-Starling mechanism) in survivors. Nonsurviving patients, even with a low LVEF, are less likely than survivors to have compensatory LV dilation and therefore not able to maintain SV. Thus, nonsurviving patients depend on increased HR to maintain CO.<sup>24</sup> When HR can no longer maintain CO, the patient dies.

By 24 hours after the onset of hypotension, surviving patients show normal HR, SVR, and CO; whereas nonsurviving patients (on average) have significantly more tachycardia, increased CO, and decreased SVR. Thus, patients who maintain the hyperdynamic state for more than 24 hours have a poorer prognosis. In fact, over two thirds of nonsurviving patients have a normal or increased CO immediately prior to death. Most early deaths following onset of septic shock are caused not by decreased CO but by refractory hypotension from decreased SVR, whereas only a minority of early deaths are caused by decreased CO. Thus, the peripheral vascular abnormality is more det-

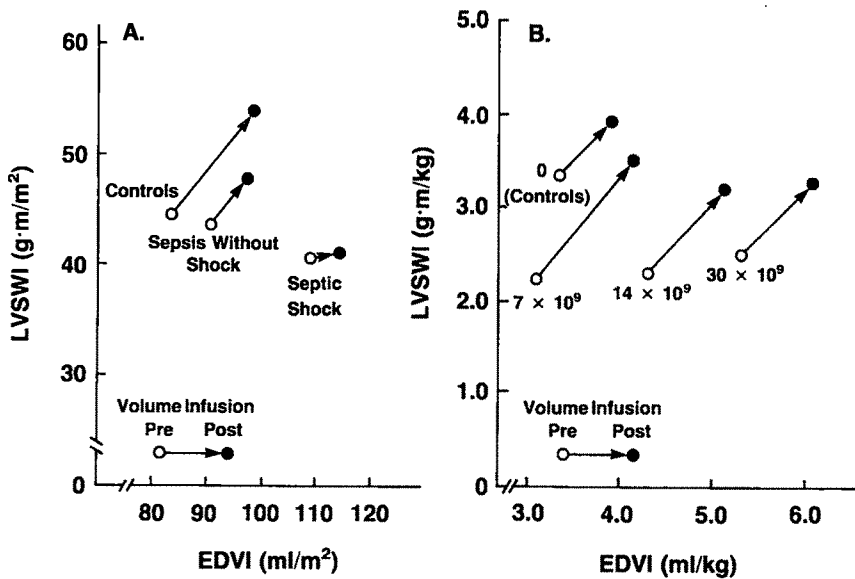


Figure 2. Frank-Starling curves of (A) humans with septic shock compared with critically ill controls, and (B) the canine model of septic shock comparing increasing doses of intraperitoneal bacteria. Mean EDVIs and LVSWIs are plotted prevolume and postvolume infusion. In both A and B, septic patients or animals have Frank-Starling curves shifted downward and to the right compared with controls. (Modified from Og-nibene FP, Parker MM, Natanson C, et al: Depressed left ventricular performance in response to volume infusion in patients with sepsis and septic shock. *Chest* 93:903, 1988; and Natanson C, Danner RL, Fink MP, et al: Cardiovascular performance with *E. coli* challenges in a canine model of human sepsis. *Am J Physiol* 254:4558-4569, 1988; with permission.)

rimental than the myocardial abnormality in the majority of early deaths caused by septic shock.<sup>25</sup>

### ETIOLOGY OF MYOCARDIAL DEPRESSION

Data indicate that sepsis-induced myocardial depression is not caused by inadequate coronary circulation, but instead is associated with a circulating factor.<sup>5, 9, 42, 45</sup> In studies at the NIH, data from coronary sinus catheters in septic patients revealed normal coronary blood flow, net myocardial lactate extraction, and increased oxygen supply to the myocardium. Thus, these patients had no evidence of ischemia as a cause of the myocardial depression. However, septic patients with depressed LVEF were found to have a circulating factor (with a molecular weight about 10,000 Daltons) in their serum that depressed myocardial cells of newborn rats *in vitro*. This substance was not found in critically ill controls or surviving patients of septic shock 7 to 10 days later. Thus, reversible myocardial dysfunction in patients with septic shock may be caused by a circulating mediator and not, in the majority of patients, by coronary insufficiency.

## COMPARISONS OF HUMAN SEPTIC SHOCK WITH HEMODYNAMIC ABNORMALITIES IN OTHER FORMS OF SHOCK

Figure 3 depicts the cardiovascular pathways of shock from several etiologies: septic, cardiogenic, extracardiac obstructive, and oligemic shock. Cardiogenic shock patients have severely reduced myocardial contractile function (secondary to myocardial damage), decreased CO, and reduced systemic perfusion. Patients with extracardiac obstructive shock have either an increased afterload against which the heart must contract (for example, massive pulmonary embolism obstructing the right ventricle) or restricted ability of the heart to fill during diastole causing inadequate preload (for example, pericardial tamponade). Oligemic shock results from inadequate preload (for example, from hemorrhage, protracted vomiting, or diarrhea) that causes decreased CO and hypotension. In these three forms of shock (cardiogenic, extracardiac obstructive, and oligemic), a decreased CO is the final part of the pathway leading to shock.

Septic shock produces two abnormalities: a peripheral vascular defect and myocardial dysfunction (see Fig. 3). With septic shock, a

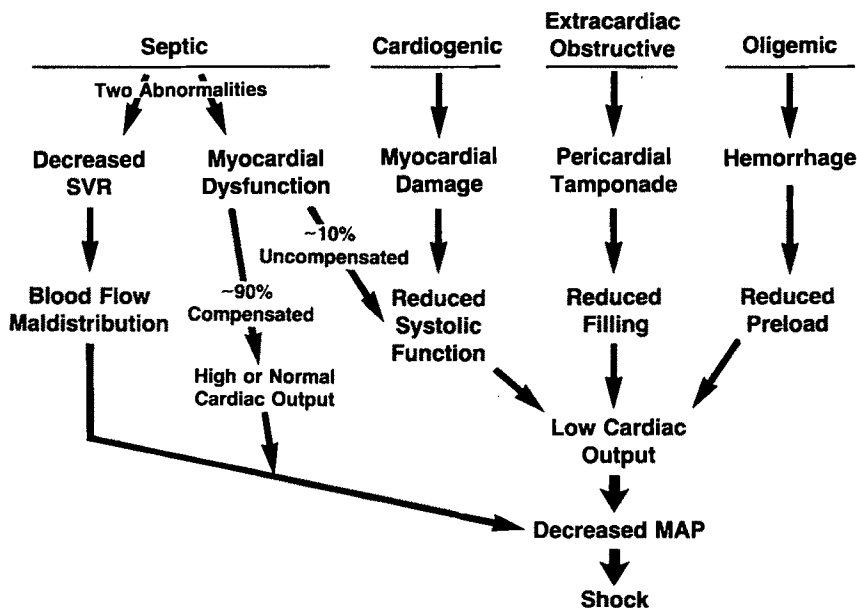


Figure 3. Pathways leading to shock for different etiologies. For cardiogenic, extracardiac obstructive, and oligemic shock, the pathway to hypotension and shock is via a low CO. In contrast, with septic shock only 10 per cent of patients have low CO leading to shock. The majority of patients with septic shock have high or normal CO, and vascular redistribution leads to hypotension.

form of distributive shock, vascular redistribution and decreased impedance to flow produce a low SVR and hypotension. This vascular abnormality occurs concurrently with myocardial dysfunction. As stated previously, we and others have shown that patients in septic shock have both depressed LVEF and LV dilation. In the majority of patients (>90 per cent), the myocardial abnormality is compensated for by sepsis-induced LV dilation that produces a normal or high SV and CO. In a minority of patients (approximately 10 per cent), myocardial dysfunction is so severe that it produces cardiogenic shock superimposed on septic shock, which is characterized by a low CO and hypotension.

## **PATHOGENESIS OF SEPTIC SHOCK**

Figure 4 shows the pathogenesis of human septic shock beginning with the source of infection and ending in death. More than 90 per cent of nonimmunocompromised patients have a diagnosable site of infection. In most cases, the site is clinically apparent as one of the following: pneumonitis, pyelonephritis, peritonitis, cholecystitis, meningitis, intravascular catheter infection, meningitis, or abscess formation in skin or bowel.<sup>32, 37, 38</sup> However, only 50 per cent of septic patients with granulocytopenia (<500 neutrophils per mm<sup>3</sup>) have a diagnosable site of infection. One hypothesis is that neutropenic patients are often infected from small, clinically obscure areas of damage to their own skin or bowel through which micro-organisms or their toxins leak into the circulation.

Recent evidence suggests that the cardiovascular abnormalities and the multiple organ system dysfunction found in septic shock are probably not directly caused by micro-organisms, but in part by the release of harmful endogenous substances (for example, tumor necrosis factor [TNF], interleukin-1 [IL-1]) in response to exogenous toxins (endotoxins and exotoxins). Controlled experiments are currently underway to investigate the complex roles and interactions of these exogenous and endogenous substances in producing the abnormalities associated with septic shock (that is, maldistribution of flow through dilation and constriction of arterioles in the peripheral vascular bed; leukocyte migration and activation; platelet aggregation and microembolization; endothelial and other cell damage; and myocardial dysfunction). In summary, these mediators and toxins take part in a complex cascade of events that result in profound hemodynamic abnormalities, multiple organ system dysfunction, and ultimately death.

## **BACTERIAL FACTORS THAT MEDIATE HUMAN SEPTIC SHOCK**

### **Endotoxin**

Endotoxin is a lipopolysaccharide in the outer membrane of gram-negative bacteria.<sup>6, 7, 44</sup> Many investigators have considered endo-

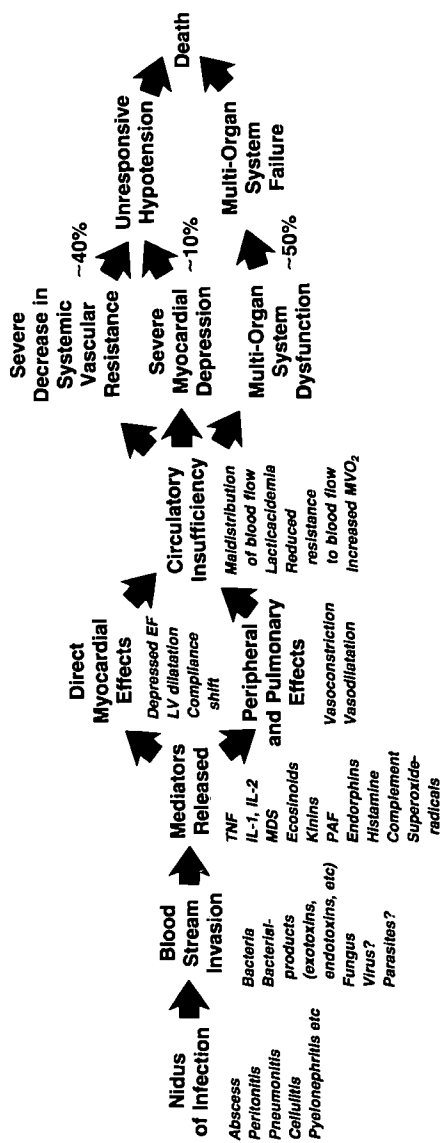


Figure 4. The pathogenesis of septic shock starting from the nidus of infection and ending in death. Blood stream invasion of bacteria, fungi, or their toxins induces release of endogenous mediators that have both direct myocardial effects and peripheral circulatory effects. These events lead to circulatory insufficiency in many organ systems and three distinct syndromes that cause death: (1) refractory hypotension due to a low SVR (approximately 40 per cent of deaths); (2) refractory hypotension from decreased CO (approximately 10 per cent of deaths); and (3) multiple organ system failure (approximately 50 per cent of deaths).<sup>8</sup> Abbreviations: TNF, tumor necrosis factor; IL-1 and IL-2, interleukin-1 and -2; MDS, myocardial depressant substance; PAF, platelet-activating factor; MVO<sub>2</sub> myocardial oxygen consumption.

toxin to be the primary mediator to induce the cardiovascular abnormalities of septic shock. In a recent study at the NIH, Danner et al<sup>6</sup> obtained serial endotoxin levels from patients with presumptive septic shock admitted to the ICU. Data from this study showed that (1) measurable endotoxemia correlated with disease severity, especially in patients with positive blood cultures; and (2) both gram-positive (organisms without endotoxin) and gram-negative (organisms with endotoxin) bacteremia produced the same cardiovascular changes with or without endotoxemia. In another study, endotoxin administration to normal volunteers resulted in the serial cardiovascular changes seen in septic shock (decreased mean arterial pressure [MAP], SVR, and LVEF; and increased CO, HR, and LVEDV).<sup>51, 52</sup> The results of these two studies suggest the following: because endotoxin alone can produce the cardiovascular abnormalities of septic shock, and because circulating endotoxin in patients with spontaneous septic shock correlates with a poor outcome, endotoxin is probably an important pathogenic mediator in some bacterial infections. Nevertheless, the fact that gram-positive bacteria can produce the cardiovascular abnormalities of septic shock without endotoxemia suggests that endotoxin is not the only mediator to produce septic shock.

### Other Bacterial Toxins

Gram-negative bacteria produce a number of enzymes and toxins (other than endotoxin) that are pathogenic in animals and that may have an important role in producing septic shock. Alpha-hemolysin, a toxin of *Escherichia coli* as well as other gram-negative bacteria, affects cell membranes causing lysis and produces lung edema and mortality in mice.<sup>50</sup> Exotoxin A, secreted by approximately 90 per cent of *Pseudomonas aeruginosa* isolates, may function synergistically with endotoxin to induce septic shock.<sup>1, 21</sup> Gram-positive bacteria possess common cellular components that have toxic effects and produce exotoxins that are pathogenic in a variety of clinical syndromes. Cell wall components such as peptidoglycans, myramyl dipeptide, and lipoteichoic acids have also been implicated in septic shock.<sup>58</sup> These toxins have a variety of effects: activating complement, producing shock, and priming neutrophils and macrophages to enhance stimulated release of toxic oxygen radicals.<sup>19, 48</sup> Exotoxins from gram-positive bacteria that are pathogenic in human disease include toxic shock syndrome toxin-1, multiple staphylococcal enterotoxins, and streptococcal exotoxins.<sup>49</sup> These substances are known to be pathogens in toxic shock syndrome and food poisoning, but some may also have a direct role in septic shock or the lethality of endotoxin or endogenous mediators.<sup>35</sup> To date, several assays have demonstrated toxic effects of gram-positive bacterial products, indicating that these toxins may play an important role in the pathogenesis of gram-positive septic shock.

## HOST FACTORS THAT MEDIATE HUMAN SEPTIC SHOCK

### Tumor Necrosis Factor

TNF, a 10- to 20-kilodalton protein made by macrophages, may also have a role in the pathogenesis of septic shock. When endotoxin was administered to normal human volunteers, it produced measurable circulating TNF at 60 and 90 minutes after the endotoxin administration.<sup>15</sup> In a variety of animal models, TNF administration can produce cardiovascular dysfunction, multiple organ system failure, and lethality.<sup>53</sup> In addition, pretreatment with either monoclonal or polyclonal antibodies to TNF has been protective when given to animals challenged with gram-negative bacteria or endotoxin.<sup>2, 54</sup> These data suggest that circulating TNF, which may be released by the host in response to circulating endotoxin or viable bacteria, is an important pathogenic mediator in septic shock.

### Interleukin-1 and Interleukin-2

Like TNF, IL-1 is produced by macrophages in response to endotoxin or viable micro-organisms.<sup>11</sup> Response to IL-1 depends on the animal model and experiment, but may include fever, hypotension, decreased SVR and activation of T-lymphocytes, and stimulation of release of other lymphokines.<sup>10, 35</sup> When administered to rabbits, IL-1 was found to be synergistic to TNF in producing the hemodynamic effects of septic shock.<sup>35</sup> Ibuprofen, a cyclo-oxygenase inhibitor, was able to inhibit the hemodynamic effects induced by IL-1, suggesting that IL-1 works via a prostaglandin pathway.

IL-2 is produced by T-lymphocytes and has been used recently to treat certain human cancers.<sup>47</sup> The IL-2 molecule has been shown to enhance natural killer cell cytotoxicity and to increase cytotoxicity against tumor cells. In a recent study in humans, the hemodynamic effects of IL-2 was evaluated while it was used as an antitumor drug. This study showed that IL-2 decreased MAP, SVR, and LVEF; and increased CO, HR, and LVEDV.<sup>33</sup> These cardiovascular abnormalities are similar to those produced by human septic shock, suggesting that IL-2 may be an important endogenous mediator of the cardiovascular abnormalities of human septic shock.

### Other Mediators

Other substances implicated in the pathogenesis of septic shock are complement, myocardial depressant substance (MDS), kinins, endorphins, eicosanoids, platelet-activating factor, superoxide radicals, and other lymphokines.<sup>4, 12, 14, 22, 46</sup> In human studies, complement activation has been associated with septic shock and levels of C5a (a complement factor that mediates anaphylaxis), which have been correlated with decreases in SVR in septic shock patients.<sup>34</sup> In other studies, MDS has been found (by a rat myocardial cell assay) in the acute phase sera of patients with septic shock.<sup>42, 46</sup> Furthermore, in vitro MDS activity has been correlated with in vivo decreases in

LVEF, left ventricular dilation, and increases in circulating lactate. Although all of these mediators may play a pathogenic role in septic shock, they probably interact in a complex fashion. Thus, understanding how these mediators affect the hemodynamic and multiple organ system dysfunction of septic shock will require further study.

### **INSIGHTS FROM A CANINE MODEL THAT SIMULATES THE CARDIOVASCULAR ABNORMALITIES OF HUMAN SEPTIC SHOCK: HEMODYNAMICS, MICROBIOLOGY, AND TREATMENT**

In previous animal models of septic shock, an intravenous bolus of bacteria or endotoxin was administered. Because of the rapid administration of toxin, data from these models did not accurately reproduce the serial cardiovascular changes seen in human septic shock.<sup>16</sup>

At the NIH, a canine model was developed whereby bacteria are implanted in a fibrin clot, which is surgically inserted into the peritoneal cavity.<sup>26</sup> This procedure causes a slow release of bacteria and toxins, and thus more closely simulates the course of many human bacterial infections. In this animal model, the dogs are studied serially over 2 to 4 weeks, the time period when cardiovascular changes of human septic shock occur. To compare the cardiovascular response in these animals to that in humans, we use radionuclide heart scan LVEFs and pulmonary artery catheter pressure and thermodilution flow measurements. In addition, the dogs are given no intravenous or inhalation anesthesia post-clot implantation to prevent any distortion of the cardiovascular changes. Furthermore, the animals are studied before and after volume infusion, as fluid resuscitation is important therapy in human septic shock.

#### **Similarity to the Cardiovascular Pattern of Human Septic Shock**

In this animal model, the infected peritoneal clot produces a hemodynamic pattern of systolic and diastolic changes similar to that of human septic shock (Figs. 1A and B, 2A and B). Two to 4 days post-infection, the dogs have a decreased LVEF; with adequate fluid resuscitation, dogs have LV dilation, high CO and low SVR levels. In surviving animals, these hemodynamic changes reverse to normal in 7 to 10 days.<sup>27</sup>

Use of this canine model has allowed us to perform detailed studies of systolic function under controlled circumstances. We found that the depressed LVEF correlated with decreases in both load-independent and load-dependent measures of myocardial contractility. Frank-Starling plots (a load-dependent measure) and end-systolic volume pressure plots (a load-independent measure) showed decreased LV function that corresponded, both in time course and magnitude, to the decreased LVEF (Fig. 2B).<sup>26</sup>

In this model, we found that even though systolic myocardial

function decreased, SV and CO increased or remained normal with adequate fluid resuscitation.<sup>26</sup> This model also provided information from LV volumes about diastolic function that helped us resolve the discrepancy between decreased systolic function and increased or normal CO. Specifically, we found that at 30 to 40 hours post-septic clot implantation, the LV dilates without increasing pressure, and LV dilation maintains SV and CO (a larger heart despite a low EF maintains SV via the Frank-Starling mechanism) (Fig. 5). This finding indicates that LV dilation is the appropriate diastolic compensatory response to a sepsis-induced LV systolic abnormality (decreased LVEF). The observation that LV dilation occurs without change in pressure suggests a sepsis-induced compliance change (that is, increased compliance).<sup>26</sup> The time course and pattern of these sepsis-induced systolic and diastolic changes are remarkably similar in humans and dogs, suggesting a common mammalian hemodynamic response to infection.

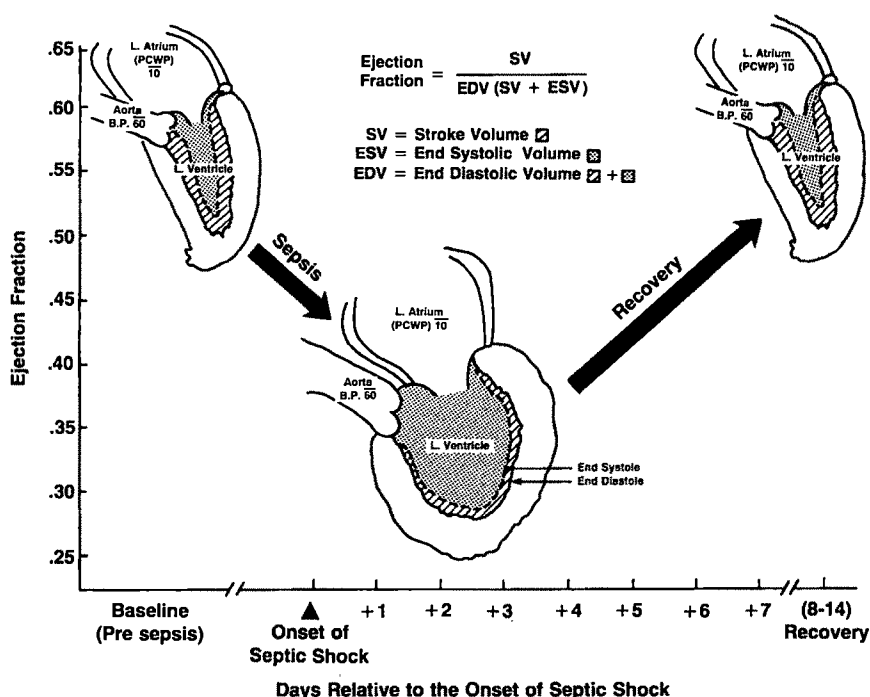


Figure 5. Cardiac output is maintained despite depressed EF during septic shock. The three left ventricles depict the serial changes during septic shock from pre-sepsis (baseline), day 2 to 4 of sepsis, and post-sepsis (recovery). The shaded area is the end-systolic volume, the hatched area is the stroke volume, combined they are the end-diastolic volume. On day 2 to 4 of sepsis, the EF falls, but because the heart is dilated (large EDV), the stroke volume does not change. (Modified from Natanson C, Parillo JE: Septic shock. *Anesth Clin North Am* 6:73-85, 1988; with permission.)

### Factors Associated with the Bacteria Affecting the Model

Using this canine model, we altered the dose, type, and viability of the bacterial infection to learn more about the role of the infecting agent in producing cardiovascular changes and mortality. When increasing the dose of bacteria in the intraperitoneal clot, we found corresponding progressive decreases in LVEF and downward shifts on Frank-Starling (Fig. 2B) and end-systolic volume/pressure LV function plots.<sup>24</sup> Not surprisingly, the highest bacterial dose ultimately caused death. In surviving animals, increasing bacterial dose corresponded to progressive LV dilation, but not to decreases in CO. LV dilation was associated with survival and maintenance of SV and CO, suggesting an important diastolic compensation (LV dilation) for sepsis-induced systolic dysfunction. Thus, dose is an important factor affecting the cardiovascular abnormalities of septic shock.

Bacterial type and viability were also important variables affecting the cardiovascular changes and mortality of septic shock.<sup>27</sup> In this study, we compared the same dose of *Staphylococcus aureus* (serotype 8), *Escherichia coli* (06:H1:K2), and *Escherichia coli* (086:H8) and found that *S. aureus* produced the greatest mortality and hemodynamic dysfunction, while *E. coli* (06:H1:K2) produced intermediate results, and *E. coli* (086:H8) produced the least mortality and hemodynamic dysfunction. In the same study, we also compared nonviable and viable bacteria (again at the same dose) and found that viable bacteria produced greater lethality and hemodynamic dysfunction. Nevertheless, all bacteria (either nonviable or viable, or gram-positive or gram-negative) produced the same pattern and time course of hemodynamic changes. These findings show that structurally and functionally distinct micro-organisms produce the same cardiovascular abnormalities, indicating that septic shock syndrome has a final common pathway of injury.

### Mediators of Septic Shock in the Canine Model

Endotoxin, a lipopolysaccharide in the outer membrane of gram-negative bacteria, has been proposed as a primary pathogenic mediator in all types (bacterial and nonbacterial) of septic shock as mentioned previously. Using the canine model, we evaluated this hypothesis in multiple experiments.

In one study, we implanted *S. aureus*, a gram-positive organism without endotoxin, in dogs and found that it produced the same cardiovascular changes seen in animals challenged with *E. coli*, a gram-negative organism with endotoxin.<sup>27</sup> Using a sensitive chromogenic limulus lysate assay, we measured serial endotoxin levels in these dogs. In the dogs given *S. aureus*, we found no endotoxemia. Thus, endotoxemia from the infecting bacteria or from endogenous sources (for example, the patient's "leaky" bowel wall) is not always found in the septic shock syndrome. These data indicate that endotoxin is not the universal mediator of septic shock.

The finding that circulating endotoxin was not necessary to pro-

duce septic shock, prompted us to examine whether endotoxin alone could produce these cardiovascular changes. Using purified endotoxin in intraperitoneal clots, we found that this toxin produced the same cardiovascular abnormalities of viable bacterial clots. Thus, although endotoxin or endotoxemia is not necessary to produce septic shock, endotoxin is sufficient and probably one of many bacterial toxins capable of producing this syndrome.<sup>27</sup> These findings are remarkably similar in human and canine septic shock.

In another study, we examined the ability of two different *E. coli* strains to produce endotoxemia and lethality in the canine model.<sup>17</sup> In this study, dogs received either *E. coli* (06:H1:K2), an organism with virulence factors associated with human infection (for example, hemolysis, serum resistance, and encapsulation), or *E. coli* (086:H8), an organism not associated with these factors. Over 28 days, serum endotoxin levels were measured serially. Both strains of *E. coli* produced the cardiovascular depression typical of human septic shock. However, although similar doses were given, the organism with virulence factors associated with human disease produced greater lethality and more profound and prolonged hemodynamic changes. Paradoxically, endotoxin levels were greater in dogs receiving the nonvirulent organism. These data indicate that the virulence factors (hemolysis, serum resistance, encapsulation) of the organism, and not the level of endotoxemia, are most important in determining morbidity in some gram-negative infections.<sup>17</sup>

Recent evidence suggests that the endogenous toxins produced in response to multiple infecting agents may be one mechanism of the final common pathway of injury in septic shock. These mediators include TNF, IL-1 and IL-2, complement, MDS, eicosanoids, endorphins, platelet-activating factor, kinins, and superoxide radicals as mentioned previously.<sup>4, 12, 14, 22, 46</sup> In one study, we infused TNF intravenously in dogs and found that it caused all of the progressive decreases in cardiovascular function produced by viable bacteria over 7 to 10 days.<sup>30</sup> In a similarly designed study, high doses of IL-1 produced minimal hemodynamic effects and none of the serial changes seen with viable bacteria or TNF.<sup>29</sup> These data indicate that TNF may be one important endogenous mediator of septic shock, whereas IL-1 does not act alone to produce the characteristic hemodynamic changes in septic shock.

### Clinical Therapies in the Canine Model

Using the canine model, we evaluated two conventional therapies, cardiovascular support and antibiotics, for septic shock.<sup>31</sup> A group of dogs with septic shock were given cardiovascular support for 3 days consisting of fluids and dopamine titrated to maintain a normal MAP, a therapy typically given to humans with septic shock. Some dogs were also given antibiotic therapy for 5 days consisting of combined cefoxitin and gentamicin. Dogs receiving both therapies had a 43 per cent survival rate, those receiving neither therapy had 0 per cent survival. Dogs receiving either antibiotic therapy alone or car-

diovascular support alone had 13 per cent survival. Thus, we deduced that both therapies are equally important for survival and that the chance for survival is greatest when the two therapies are combined.

In a controlled, randomized study, we evaluated whether plasmapheresis improves survival in canine septic shock.<sup>28</sup> We chose to examine pheresis because of the possibility that it could eliminate toxic mediators of the septic shock syndrome by removing the non-cellular blood components. To test this hypothesis, we implanted lethal doses of bacteria intraperitoneally in dogs treated with fluids and antibiotics. Three study groups were prospectively defined: (1) a control group that had no further therapy; (2) a sham pheresis group that had plasmapheresis at 5 and 24 hours post-clot implantation and had their own infected plasma immediately returned; and (3) a true pheresis group that had plasmapheresis at 5 and 24 hours and had this volume of plasma replaced with uninfected fresh frozen canine plasma. Unexpectedly, the control group and the sham pheresis group had higher survival rates and less hemodynamic depression than the true pheresis group. Thus, plasmapheresis worsened hemodynamics and increased mortality, suggesting that removal of infected plasma through a plastic membrane was more harmful than beneficial to these animals.

By enabling us to perform controlled detailed studies of septic shock, this animal model will help us understand the pathophysiology of the disease and provide us with a preclinical tool to investigate new therapies.

## TREATMENT OF HUMAN SEPTIC SHOCK

Tables 1 and 2 describe the treatment of human septic shock and three goals for therapy: (1) to eradicate the organism with antibiotics and to remove the focus of infection (drainage of abscesses, debridement, and so forth) where appropriate; (2) to administer agents that neutralize exogenous and endogenous toxic substances; and (3) to provide supportive care for multiple involved organ systems.

### Eradication of Infection

As soon as the clinician considers a possible diagnosis of septic shock, the patient should be cultured and treated empirically with broad-spectrum antibiotics. The sites for culture (for example, CSF, skin abscess) will depend on findings from a detailed history, physical examination, and preliminary roentgenograms and laboratory data. Prior to administering empiric antibiotics, the clinician should optimally obtain a minimum of two blood cultures drawn from different sites, as well as sputum, urine, and cultures from other possible sources of infection (for example, CSF, peritoneal fluid, pleural fluid). If intravascular catheters are possible sites of infection, immediate replacement of these catheters should be considered. If the nidus of infection is not found after routine investigation, additional diagnostic

Table 1. *Septic Shock Therapy: Three Goals*


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|                                                                                       |
|---------------------------------------------------------------------------------------|
| I. To eradicate nidus of infection                                                    |
| Empiric antibiotics (broad coverage)                                                  |
| Attempt to identify source of infection                                               |
| Remove focus of infection: foreign body, remove; abscess, drain                       |
| II. Administration of agents to neutralize toxins                                     |
| A. Investigational approaches in humans                                               |
| Antiserum to J-5 <i>E. coli</i>                                                       |
| Immune serum globulin (high titers to common bacterial pathogens)                     |
| Antiendotoxin immunoglobulins                                                         |
| Corticosteroids                                                                       |
| B. Proven beneficial in animal septic shock                                           |
| High-dose naloxone                                                                    |
| Prostaglandin E <sub>1</sub>                                                          |
| Indomethacin                                                                          |
| Lipid-X                                                                               |
| Antiserum to tumor necrosis factor                                                    |
| Anticomplement (C5A) antibodies                                                       |
| Ibuprofen                                                                             |
| Protein C                                                                             |
| III. Cardiovascular supportive therapy                                                |
| A. A medical intensive care setting                                                   |
| Full-time critical care nurses, physicians, and technicians                           |
| Intra-arterial monitoring                                                             |
| Accurate                                                                              |
| Therapy based on immediate beat-to-beat analysis                                      |
| Frequent arterial blood gas sampling                                                  |
| Right heart catheterization                                                           |
| Confirm correct diagnosis                                                             |
| Base therapy on accurate cardiac filling pressure and flow measurements               |
| Cardiac rhythm monitoring                                                             |
| Antiarrhythmic agents                                                                 |
| Electrical cardioversion                                                              |
| B. Fluid resuscitation                                                                |
| Eliminate other causes of cardiovascular depression                                   |
| Correct: Anemia, hypoxemia, acidosis, hypophosphatemia, hypocalcemia, hypoalbuminemia |
| If MAP $\leq 60$ , optimize preload                                                   |
| Volume expansion to PCWP $\geq 15$ –18                                                |
| Crystalloids/albumin/synthetic colloids                                               |
| Avoid pulmonary edema                                                                 |
| C. Pressors                                                                           |
| If MAP $\leq 60$ despite PCWP $\geq 15$ to 18, begin pressors (see Table 2)           |

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tests should be considered. Once the source of infection is determined and the infecting agents identified, the clinician can then limit antibiotics to treat the particular organisms involved.

### Mediator-Specific Therapy

Several recent studies are investigating new therapies for septic shock that attempt to neutralize exogenous and endogenous mediators by enhancing clearance of or producing tolerance to these mediators. Some of these new therapies are currently being investigated in humans. Treatments such as monoclonal antibodies to parts of the endo-

Table 2. *Pressor Therapy*

| INDICATION<br>(MAP $\leq$ 60, PCWP $\geq$ 15-18)     | PRESSOR        | DOSE<br>( $\mu$ g/kg/min) | CARDIAC<br>STIMULATION | VASOCONSTRICTION | VASODILATATION |
|------------------------------------------------------|----------------|---------------------------|------------------------|------------------|----------------|
| $\uparrow$ or normal CO                              | Dopamine       | 1-10<br>10-20             | ++<br>+++              | +                | ++             |
| Dopamine failure                                     | Norepinephrine | 2-8†                      | ++                     | +++              | +              |
| Arrhythmias                                          | Phenylephrine  | 20-200†                   | 0                      | +++              | 0              |
| $\downarrow$ CO, norepinephrine failure              | Epinephrine    | 1-8†                      | +++                    | +++              | ++             |
| $\downarrow$ CO, combine with norepinephrine therapy | Dobutamine     | 1-10                      | +++                    | +                | ++             |
| $\downarrow$ CO                                      | Isoproterenol  | 1-4†                      | +++                    | +                | +              |

† Dose is  $\mu$ g per minute.

toxin molecule, naloxone, prostaglandin inhibitors, lipid X (an analog of endotoxin), and antibodies to TNF have all shown some efficacy in animals. This area of investigation shows much promise, although currently no therapy has yet been widely accepted for clinical use.

In a recent human study, serum from normal volunteers previously vaccinated against J5 *E. coli* was given to patients with septic shock and found to decrease patient mortality.<sup>61</sup> The reasons for this protection are controversial, and, though the results of this study were published several years ago, passive immunization is not yet available for clinical use.<sup>62</sup>

Previously, corticosteroid therapy had also been advocated as a method of improving survival in septic shock (perhaps by modulating the effects of mediators on the circulation). However, two recent clinical trials showed that when corticosteroids were administered to patients in septic shock (even within 2 hours of onset), the steroid failed to enhance survival and may have actually been detrimental to a subset of patients with renal failure.<sup>3, 55</sup>

### Cardiovascular Support

Most clinicians agree that the best initial therapy for patients with septic shock is fluid resuscitation. In addition, these patients should be observed continuously in an intensive care unit and constantly reassessed while empiric fluid therapy is given. Intra-arterial and pulmonary arterial catheters help clinicians manage septic shock patients. Because these catheters allow accurate determination of systemic and cardiac filling pressures, fluid therapy is based on reliable serial hemodynamic data. At the NIH, we use a MAP greater than 60 despite adequate LV filling pressure (PCWP of 12 to 18 mm Hg) as our initial goal for cardiovascular support of septic shock. As patients may receive 15 to 20 L of crystalloid fluid during the first 24 hours of septic shock, pulmonary artery catheters may be necessary to assess the hemodynamic effect of the rapid administration of large quantities of fluid that may be required to reverse the sepsis-induced hypotension (Fig. 6). These catheters enable the clinician to administer fluids and monitor LV filling pressure (PCWP) serially, thus avoiding filling pressures that could produce pulmonary edema (PCWP > 18 to 20).

The type of fluid (crystalloid, albumin, synthetic colloid, or blood products) given probably matters less than whether it is titrated to the appropriate PCWP and MAP. At the NIH, we commonly use crystalloid solutions (lactated Ringer's or saline) because they are safe and inexpensive. Colloid solutions are more rapid plasma expanders, but are more expensive, can alter platelet function, and may interfere with cross-matching of erythrocytes. In addition to crystalloid solutions, we give packed red blood cells until the hematocrit is approximately 35 per cent and give 25 per cent albumin for patients with serum albumin levels less than 2 g per dl.

If the MAP does not increase rapidly to greater than 60 mm Hg after the PCWP is increased to 15 to 18 mm Hg, we begin pressor agents. Pressor agents are chosen for their specific effects on MAP,

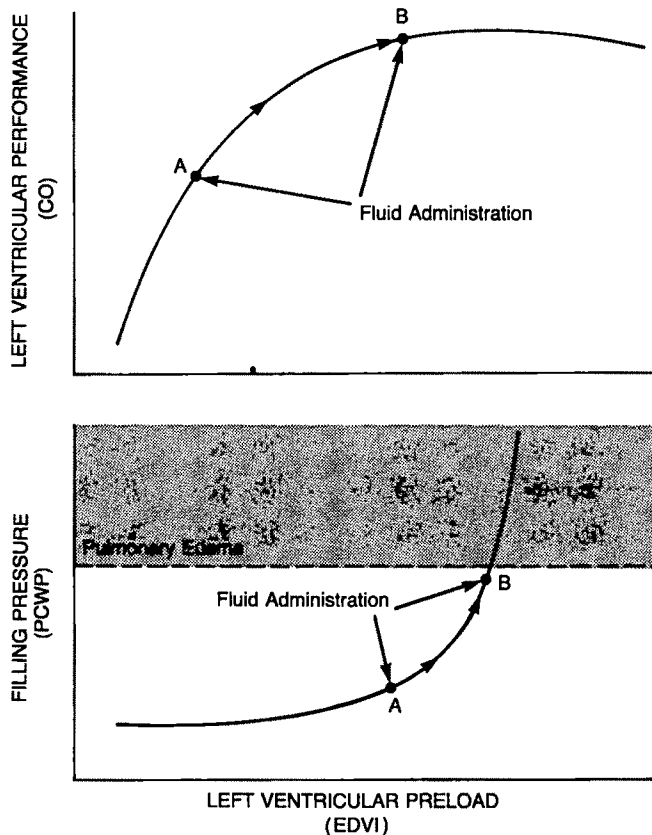


Figure 6. The upper graph shows the Frank-Starling relationship, that is, LV performance (CO) versus preload (PCWP). In the upper graph, as preload is increased from point A to B, there is a corresponding increase in ventricular performance. The lower graph depicts the LV pressure volume relationship in diastole. In the lower graph, increasing preload, results in corresponding increases in PCWP. Fluid administration, when guided by serial thermodilution pulmonary artery catheter CO and PCWP measurements, can optimize LV performance while avoiding pulmonary edema (shaded area of lower graph).

HR, CO, and renal blood flow (see Table 2). Initially, we start with dopamine and titrate it up to a maximum of 20  $\mu\text{g}$  per kg per minute. If this level is not adequate to maintain MAP greater than 60 and to avoid arrhythmias occasionally seen with high dose ( $> 20 \mu\text{g}$  per kg per minute) dopamine, we add norepinephrine and lower the dopamine dose to 1 to 2  $\mu\text{g}$  per kg per minute to improve renal perfusion. For most patients, either dopamine alone or dopamine (in low renal vasodilating doses) with norepinephrine are adequate pressor therapy. In the atypical patient with low CO or in patients who do not respond well to norepinephrine, epinephrine may be a better choice because it increases CO as well as MAP. In patients who respond to

norepinephrine or dopamine with tachyarrhythmias, we often use phenylephrine because it has potent peripheral vascular effects with no chronotropic effects. During pressor therapy, serial hemodynamic evaluations often help the clinician evaluate the need for additional fluid and pressor therapy to improve cardiovascular performance.

## SUMMARY

Septic shock is an increasingly common disorder that produces profound dysfunction of multiple organ systems and is lethal in approximately 50 per cent of patients. Early deaths are usually caused by refractory hypotension with a low systemic vascular resistance (SVR). Deaths occurring later are usually caused by sepsis-induced multiple organ system failure syndrome.

A distinct pattern of hemodynamic change occurs during septic shock. Within the first 2 to 3 days, the LV dilates, LVEF decreases, and alterations on the Frank-Starling and end-systolic pressure plots show LV dysfunction. CO usually increases or remains normal, whereas SVR decreases or remains normal. This maintenance of CO and SV in the setting of LV dysfunction is probably related to changes in diastolic function. During septic shock, the LV dilates without increasing pressure, and SV and CO either remain unchanged or increase via the Frank-Starling mechanism. Occasionally, patients with septic shock have low CO and concomitant hypotension, but this is uncommon and occurs only in patients with severe cardiac deficiency and combined septic and cardiogenic shock. In surviving patients, these cardiovascular changes reverse to normal in 7 to 10 days. Because we have also found an identical sequence of hemodynamic change in our canine model, this response may be common for all large mammals.

The pathophysiology of septic shock is complex and still not completely understood. It is believed that multiple bacterial toxins (not necessarily endotoxin) release host mediators (for example, MDS, TNF, IL-1, IL-2, complement, eicosanoids) that produce shock and death. The chemical nature of these mediators and their role in infection is still undergoing investigation.

Treatment of patients with septic shock is often optimized by immediate referral to the intensive care unit. Patients should receive broad-spectrum antibiotics, and intra-arterial and pulmonary artery catheters to help guide resuscitative therapy with fluids and pressors. Initially patients should be given volume resuscitation. However, if hypotension persists after adequate volume resuscitation, patients should be given pressor agents selected for their effects on peripheral resistance, contractility, and HR.

At the NIH medical intensive care unit, we use the following algorithm to treat patients in septic shock. We correct all laboratory abnormalities including anemia, acidosis, hypoalbuminemia, and hypoxia. We administer crystalloid as initial resuscitative therapy to in-

crease preload while simultaneously measuring serial hemodynamic variables (PCWP, CVP, SVR, CO, and MAP). If PCWP is greater than or equal to 15 and hypotension persists, we administer a vasopressor. Initially we administer dopamine in low doses (1 to 10  $\mu\text{g}$  per kg per minute) to preserve renal blood flow. If hypotension persists with dopamine in doses greater than 20  $\mu\text{g}$  per kg per minute, we add norepinephrine and turn dopamine down to 1 to 2  $\mu\text{g}$  per kg per minute to avoid adverse effects of dopamine in high doses (tachycardia and atrial arrhythmias). In patients with cardiac arrhythmias, we use phenylephrine instead of norepinephrine because of its predominant alpha-adrenergic agonist effects. In the rare circumstances of patients with low CO despite adequate preload, we administer epinephrine for its potent beta- and alpha-adrenergic effects.

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## Nosocomial Pneumonia

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Nosocomial infections are those developing in hospitalized patients in whom the infection was not present or not incubating at the time of admission to the hospital.<sup>44</sup> Urinary tract infections are the most common hospital-acquired infection.<sup>35</sup> Within the critical care environment, hospital-acquired lung and bloodstream infections surpass urinary tract infections.<sup>8</sup>

The incidence of nosocomial pneumonia in the intensive care unit (ICU) is largely dependent on the type of ICU. A Coronary Care Unit (CCU) that primarily monitors abnormal rhythms and does not manage cardiogenic shock or pulmonary edema should have essentially no hospital-acquired pneumonias. A 12 per cent incidence of hospital-acquired pneumonia has been reported for medical ICUs and a 22 per cent incidence for a mixed medical-surgical ICU.<sup>44</sup>

It has been projected that there are between 225,000 and 380,000 cases of hospital-acquired pneumonia each year.<sup>46</sup> Craig and Connelly<sup>8</sup> examined 670 patients admitted to six community hospital ICUs. They found that 8.8 per cent of those patients developed a nosocomial pneumonia and had an average stay in the ICU three times longer than control patients and a mortality rate four times higher.<sup>8</sup> One author has predicted the annual health care cost of hospital-acquired pneumonia at greater than \$1 billion.<sup>46</sup>

The usual organisms (60 to 80 per cent) causing hospital-acquired pneumonia are aerobic gram-negative rods. *Pseudomonas*, *Klebsiella*, *Enterobacter*, *Escherichia coli*, and *Proteus* predominate. *Staphylococcus aureus* accounts for only about 10 to 15 per cent of nosocomial pneumonias.<sup>45</sup>

Patients most susceptible to hospital-acquired pneumonia are those with progressive critical illness. Johanson et al<sup>22</sup> prospectively evaluated 213 patients admitted to a medical ICU and noted that coma, hypotension, expectoration of sputum, the use of an endotracheal tube, acidosis, azotemia, and either leukocytosis or leukopenia were most closely associated with an episode of nosocomial pneumonia. That

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study was done 17 years ago, but the basic principle noted then is still valid. The more critically ill an ICU patient and the more systems in failure the more likely they are to develop a hospital-acquired pneumonia.

Intubated patients on mechanical ventilation are particularly susceptible to pneumonia. Within the first few days of placing an endotracheal tube one notes the presence of gram-negative bacteria in tracheal secretions. Eventually polymorphonuclear leukocytes appear in the gram stain of the sputum. Fever begins and on chest roentgenogram there is an appearance of a new infiltrate. The diagnosis of hospital-acquired pneumonia and timing of antibiotic therapy is a significant dilemma in critical care. One does not want to treat a colonization and lead to an overgrowth of antibiotic resistant organisms. Alternatively, one does not want to wait too long in administering antibiotics, particularly in debilitated patients, and allow the organism to get too strong a foothold in the lung. These issues are reviewed in this article with suggestions for diagnosis and management based on the last 20 years of experience of treating patients with hospital-acquired lung infections.

It has been generally held that there are four different mechanisms for hospital-acquired pneumonias.<sup>46</sup> First is inhalation of airborne organisms. Historically this was thought to be the primary route of inoculating the lung. Contaminated respiratory therapy equipment leads to the inhalation of or direct inoculation with contaminated material. Second is aspiration of oropharyngeal contents. This is presently the most popular pathogenesis for nosocomial pneumonias. Third is direct extension from a contiguous site, and fourth is hematogenous spread. The latter two are thought to be reasonably rare in comparison to the first two.

## INHALATION OF AIRBORNE ORGANISMS

Respiratory care had its early beginnings with the poliomyelitis epidemic in the late 1940s and early 1950s. By the late 1950s the first ICUs were established. The 1960s brought in an era of respiratory intensive care with the development of volume-limited ventilators and other sophisticated respiratory therapy equipment. This era also brought the first understanding of nosocomial pneumonia.

In 1968 Ringrose et al<sup>38</sup> reported an epidemic of *Serratia marcescens* infections. Nineteen patients were involved. Nine patients had infections and ten others appeared to be only colonized with *Serratia*. The source of the outbreak was improperly cleaned ultrasonic nebulizers. Other investigators such as Reinartz and Mertz<sup>36</sup> also reported outbreaks of hospital-acquired pneumonia related to respiratory therapy equipment in the 1960s.

There evolved a clear clinical concept that nosocomial pneumonias were largely iatrogenic and exogenous in nature and secondary to the introduction of organisms into patients from improperly cleaned

equipment. This concept persisted throughout most of the 1970s and resulted in numerous other publications. Thompson et al<sup>43</sup> found that 75 per cent of the bedside resuscitation bags were contaminated with bacteria. Gardner and Shulman<sup>15</sup> reported an epidemic of *Pseudomonas pickettii* from contaminated saline used for irrigation of the endotracheal tube. Likewise, Rutala et al<sup>39</sup> found that improper opening of saline vial could lead to contamination when used to irrigate the airway. Much work has been done on the factors responsible for contamination of ventilator tubing and the frequency with which ventilator breathing circuits must be changed.<sup>9</sup>

By the 1980s it became progressively clear that exogenous contamination of respiratory therapy equipment produced only sporadic outbreaks reported in the medical literature. Much knowledge had been gained about the cleaning and sterilization of respiratory therapy equipment. For many reasons, the use of disposable equipment has increased and the risk to the patient of an exogenous source for infection was significantly reduced.

Nursing protocols for endotracheal suctioning have been formulated that limit the opportunity for exogenous pneumonia. The health care provider who suctions the patients wears sterile gloves and irrigates the endotracheal tube with sterile saline from a single dose 5- to 10-mL vial. Suction kits are available that provide sterile supplies such as suction catheter, gloves, saline irrigation, and sterile fluid for clearing the suction tubing. All items are discarded when the procedure is complete.

Oxygen delivery systems frequently use sterile single-use humidifiers. The use of ultrasonic nebulizers that are difficult to clean have declined. Ventilator tubing is frequently disposable and reusable components are decontaminated with much greater sophistication than in the late 1960s.

One significant advance in decreasing blood stream infections associated with the use of pulmonary artery catheters was the sterile plastic sleeve that permits the position of the catheter to be altered. Recently, an endotracheal suction system has been marketed that packages the suction catheter in a similar sterile sleeve. The sleeve is an intrinsic part of the right angle adaptor that connects the endotracheal tube to the ventilator tubing. At any time the suction catheter can be advanced through the right angle adaptor into the endotracheal tube for a "no touch" suctioning technique. This permits closed-system suctioning, and like closed-system urine collection from a Foley catheter, is a simplified device that may reduce exogenous hospital-acquired pulmonary infection. A separate port on this system permits the injection of sterile saline from a unit dose vial for endotracheal irrigation.

Overall respiratory therapy and critical care nursing have made significant advances in the last 20 years in ICU care to limit exogenous sources of organisms causing hospital-acquired pneumonia. Unfortunately, new etiologies of lung infection have filled the void created by higher quality ICU care.

## ASPIRATION OF OROPHARYNGEAL CONTENTS

In 1981 Cross and Roup<sup>10</sup> reported the prospective evaluation of 13,086 patients of whom 914 had some sort of respiratory assistance device. They noted 108 episodes of hospital-acquired pneumonia, 70 per cent of which were aerobic gram-negative rods. Of patients with endotracheal tubes and respirators, 1.3 per cent developed a lung infection. Twenty-five per cent of patients with tracheostomies acquired pulmonary infections. Sixty-six per cent of patients with a tracheostomy and a ventilator had hospital-acquired pneumonia in this study. The author simultaneously cultured respiratory therapy equipment in the ICU but could show no correlation with the infections seen in the respiratory failure patients. He concluded "routine in-use monitoring (bacteriologic) of respiratory assistance devices does not appear warranted." Clearly there had to be some other cause for these episodes of hospital-acquired pneumonia.

That "other cause" has turned out to be aspiration of oropharyngeal contents as originally described by Atherton and White.<sup>2</sup> He prospectively followed ten patients on mechanical ventilation and cultured stomach contents and tracheal aspirates. He noted consistently that aerobic gram-negative rods developed in gastric material and subsequently could be grown from tracheal aspirates.

Subsequently, Johanson et al<sup>23</sup> demonstrated that aerobic gram-negative rods could be grown from oropharyngeal epithelial cells of respiratory failure patients in the ICU. Only 2 per cent of normal people have gram-negative rods in their oropharyngeal secretions. It has been found that at least 50 per cent of ICU patients will be colonized in the oropharynx with gram-negative rods.<sup>44</sup> There is a loss of the protective fibronectin coating over oropharyngeal epithelial cells that permits a binding of gram-negative rods to the surface of epithelial cells.<sup>46</sup> The bacteria proliferate and reach high concentrations in the oral secretions of critically ill patients.

It is speculated that small volumes of oropharyngeal secretions, dense with bacteria, leak past the cuff of the endotracheal or tracheostomy tube leading to an inoculation of the upper airway and subsequent colonization.<sup>11</sup> For the past 10 years, most ICUs have used high-volume low-pressure cuffs on endotracheal tubes to minimize lateral wall pressure and ischemia of the tracheal mucosa. The early respiratory care literature from the 1960s was replete with stories of tracheal necrosis and inominate artery perforations from low-volume high-pressure cuffs. The evolution of low-pressure cuffs for use during positive pressure ventilation seems to have permitted a better opportunity for aspiration of oropharyngeal contents.

In 1982 du Moulin et al<sup>13</sup> documented this pathway of aspiration by culturing gastric and upper airway flora in 60 consecutive respiratory failure patients. They noted the same phenomenon that Atherton had reported 4 years before, but they were the first who recognized that this was related to the iatrogenic manipulation of gastric pH for the purpose of preventing stress ulcers.

The stomach normally is not colonized with bacteria, primarily because the pH of 1 to 2 is not conducive to the growth of microorganisms. Mehta et al<sup>31</sup> looked at the pH-dependent bactericidal barrier for four aerobic gram-negative rods; *E. coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, and *Serratia marcescens*. They noted that at a pH of 2.7 or below all organisms were killed in 1.5 hours. At a pH of 3.1 or greater there was no reduction in viable bacteria over 2 hours. For the past 15 years the prevention of stress ulcers in the ICU has been based on the regulation of gastric pH to 4.0 or greater by the use of antacids and H<sub>2</sub>-receptor blockers.

In an attempt to better analyze the sequence of gastric to pharynx to lung colonization in the critically ill patient, Garvey et al<sup>16</sup> prospectively examined 25 ICU patients admitted for intubation and mechanical ventilation. All 25 patients were placed on stress ulcer prophylaxis with particulate antacid. If gastric pH remained below 4, an H<sub>2</sub>-receptor antagonist was added to the prophylactic therapy to further increase gastric pH. Nasogastric aspirate and tracheobronchial aspirate were collected three times weekly for culture. Nasogastric aspirates became positive for bacteria in all 25 patients within the first 4 days of admission to the ICU. Within 8 days of admission all patients grew *Candida* from nasogastric cultures, but these cultures usually followed positive cultures for bacteria. Nineteen per cent of the time cultures from tracheobronchial secretions were preceded by the same organisms being grown from nasogastric cultures. Thirty one per cent of the time concurrent cultures from tracheobronchial suctioning and nasogastric aspirates grew the same organisms. Twenty two per cent of the time bacteria were first grown from the lung, and 28 per cent of the time the same organisms were never grown from the lung and stomach.

The authors of this article inferred an association with bacteria in the stomach related to stress ulcer prophylaxis and bacteria in the lung causing hospital-acquired pneumonia and suggested a "detrimental effect of antacid therapy." When one is attempting to understand the pathophysiologic mechanisms of hospital-acquired pneumonia, one is left confused by the 81 per cent of patients in this study who failed to first grow the organisms from the stomach and then from the lung. In many situations bacteria from the stomach were grown at the same time, after, or not at all from the lung. Clearly, antacid therapy causes an overgrowth of bacteria in the stomach but this article fails to demonstrate that these bacteria spread first to the oropharynx and then to the lung.

## STRESS ULCER PROPHYLAXIS

Stress ulcers have been associated with critical illness for many years. Curling found such ulcers with gastrointestinal bleeding in burned patients in the 1800s. Not until the early 1970s was there much interest in documenting the association between critical illness and

abnormalities of the gastric and duodenal mucosa. Lucas et al<sup>26</sup> prospectively endoscoped patients with sepsis, shock, and trauma identifying a variety of mucosal abnormalities. They noted decreased gastric mucosal blood flow and diffuse erosions. They suggested increased gastric acid secretion in some patients.

Czaja et al<sup>7</sup> noted a 78 per cent incidence of gastric mucosal abnormalities and a 72 per cent incidence of duodenal abnormalities in burned patients. Their findings concluded that the larger the burn the greater the chance for gastrointestinal abnormalities. They suggested ischemic damage to the gastric mucosa.

Two years later McAlhany proposed neutralization of gastric acid as a prophylactic therapy for the mucosal abnormalities, ulcers, and bleeding seen by Lucas and Czaja.<sup>29</sup> He gave antacids to 24 patients who had only one episode of bleeding in comparison with 24 control patients who had six episodes of bleeding and one gastric perforation. This author titrated gastric pH to 7 by giving 60-mL doses of antacid.

Subsequent controlled studies further documented the efficacy of antacids in preventing stress ulcers in a variety of ICU patients with various types of illness.<sup>19</sup> It became clear that the creation of stress ulcers required a pH of 4.0 or below plus critical illness from sepsis, liver failure, renal failure, and so forth.<sup>37</sup> Untreated patients had an incidence of 50 per cent gastrointestinal bleeding but treated patients rarely had problems with significant ulceration and bleeding.

The manipulation of gastric pH for the prevention of stress ulcers was further aided by the availability of H<sub>2</sub>-receptor blockers. McElwee et al<sup>30</sup> and Khan et al<sup>25</sup> showed that H<sub>2</sub> blockers were as good or better than antacids in preventing stress ulcers. Halloran et al<sup>18</sup> demonstrated that the H<sub>2</sub> blocker cimetidine was significantly better than no prophylaxis in preventing stress ulcers in head trauma patients.

By the late 1980s ranitidine was the predominate prophylactic agent for stress ulcers in critically ill patients. Ranitidine seemed to have fewer side effects such as decreased drug clearance and decreased level of consciousness than were seen with cimetidine.<sup>5, 14</sup> A continuous infusion of 150 mg per 24 hours of ranitidine either in the total parenteral nutrition solution or alone was significantly less labor intensive for the ICU nurse than the hourly administration of antacids. The efficacy of manipulation of gastric pH to prevent stress ulcers was established.

In many critical care settings the use of H<sub>2</sub>-receptor antagonists as stress ulcer prophylaxis largely replaced antacid therapy because of the labor intensive process of using antacids alone even though their efficacy has been well demonstrated. The usual therapy with antacids requires the administration of 30 to 60 mL of particulate antacid down the nasogastric tube. The tube is clamped for 30 to 45 minutes and then connected to low continuous suction. At the end of 1 to 2 hours the bedside nurse again samples the nasogastric drainage and measures pH. If the pH is less than 4, she administers more antacid. A nurse caring for two patients on antacid stress ulcer prophylaxis

can spend 5 to 10 minutes per hour on the gastric mucosa of two patients. In today's shortage of ICU nursing personnel, antacids are too great a burden on nursing when the same protection can be provided by the use of H<sub>2</sub>-receptor antagonists. An additional side benefit of H<sub>2</sub>-receptor antagonists is the reduction in gastric volume when compared with patients on antacids, thus limiting gastroesophageal reflux.

### BACTERIAL COLONIZATION OF THE STOMACH

Concerns over bacterial colonization of the stomach were largely ignored by critical care physicians after the articles by du Moulin and Johansen until Driks et al<sup>12</sup> demonstrated a 23.2 per cent incidence of hospital-acquired pneumonia in patients who had their gastric pH manipulated by antacids, H<sub>2</sub> blockers, or both. When sucralfate was used as stress ulcer prophylaxis, there was a 11.5 per cent incidence of pneumonia.

Sucralfate had been demonstrated to be effective in preventing stress ulcers in critically ill patients by Borrero et al.<sup>4</sup> Sucralfate is a cytoprotective agent that forms a barrier over the gastric and duodenal mucosa and seems to prevent the harmful stress ulcer effects of acid. Sucralfate does not change gastric pH and as a result bypasses some of the concerns of bacterial overgrowth associated with antacids and H<sub>2</sub> blockers.

Closer analysis of Craven's data shows that he combined three groups of patients to compare with the sucralfate group. Some patients were on antacids alone, with a 23 per cent incidence of hospital-acquired pneumonia. Patients on antacids plus H<sub>2</sub> blockers had a 46 per cent incidence of nosocomial pulmonary infections. Interestingly, patients on only H<sub>2</sub> blockers had a 5.9 per cent incidence of nosocomial pneumonia.

If the most significant problem in hospital-acquired pneumonia is the aspiration of bacteria-containing fluid from the stomach when pH is manipulated by antacids and/or H<sub>2</sub> blockers, it is unexpected that patients on H<sub>2</sub> blockers alone had a lower incidence of pneumonia than the sucralfate group. One possible explanation for this is the effect of H<sub>2</sub> blockers on gastric volume.

### GASTRIC VOLUME

Gastric volume has been of concern to anesthesiologists for many years because of the risk of aspiration during the induction of general anesthesia for elective or emergent surgery. Manchikanti et al<sup>27</sup> demonstrated an average gastric volume in elective surgery patients of 26 to 30 mL. The pH of that material was generally less than 2.0. It has been frequently stated that the risk of acid aspiration is greatest when

the gastric volume is greater than 25 mL and the pH is less than 2.5. Most elective surgery patients then are at risk of significant acid aspiration.

This information has resulted in numerous prospective studies to evaluate the effect of various premedications on gastric pH and gastric volume.<sup>28</sup> This work has demonstrated that H<sub>2</sub> blockers will reduce by 50 to 75 per cent the gastric volume of elective surgery patients. Likewise, metoclopramide is most effective at reducing gastric volume.<sup>6, 34</sup> Other agents such as anticholinergics are minimally effective.<sup>24</sup>

The use of particulate antacids such as aluminum hydroxide and magnesium hydroxide pose a significant risk to elective surgery patients when given alone because there is an increase in gastric volume and greater opportunity for gastroesophageal reflux. Gibbs et al<sup>17</sup> demonstrated quite clearly that aspiration of particulate antacids in dogs created hypoxia and increased shunt nearly equal to that of a hydrochloric acid aspiration. In addition there was a brochopneumonia that was present in the lung of the dog 1 month later whereas the lung of the dog with an acid aspiration had returned to normal.

Another interpretation of the study by Driks et al would suggest the possibility that hospital-acquired pneumonia relates not only to gastric pH but also to gastric volume. Patients receiving antacids may have had a greater gastric volume and increased opportunity for gastroesophageal reflux.<sup>12</sup> This leads to colonization of the posterior pharynx and aspiration around the cuff of the endotracheal tube and hospital-acquired pneumonia.

## PREVENTION OF HOSPITAL-ACQUIRED PNEUMONIA

Through a better understanding of the mechanisms involved in the production of nosocomial pneumonia, clinicians have begun to formulate recommendations for prevention of this serious disorder. Historically we know respiratory therapy equipment must be properly cleaned and disinfected and used with appropriate precautions. Closed system suction devices are now available to reduce the risk of airway contamination. Closed system techniques for filling the ventilator and humidifier and draining water from the ventilator tubing have also been developed. Changing ventilator tubing every 24 to 48 hours and maintaining closed system techniques has been investigated and found to eliminate most exogenous iatrogenic causes of hospital-acquired pneumonias. Unit dose medications and saline irrigation should also be used.

In the area of aspiration of gastric contents the evidence would suggest that antacids should be eliminated from the critical care environment as a prophylactic agent. H<sub>2</sub> blockers which reduce gastric volume, should minimize the risk of hospital-acquired pneumonia. If additional therapy is needed, the cytoprotective agent sucralfate should be added to the prophylactic regimen, but H<sub>2</sub> blockers should

be the primary agent for prophylaxis because of their ability to reduce gastric volume. Low gastric volumes should minimize gastroesophageal reflux and aspiration of aerobic gram-negative rods. At the present time the H<sub>2</sub> blocker with the lowest complication rate and longest safety record is ranitidine.

The use of positive end expiratory pressure (PEEP) on all intubated patients may help reduce seepage of oropharyngeal fluids containing bacteria around the cuff of the endotracheal tube. Overinflation of the cuff on the endotracheal tube or tracheostomy tube to prevent aspiration of fluid would be unacceptable because of the risk of tracheal damage. The lateral wall pressure of the endotracheal tube cuff must be kept to less than 15 to 20 mm Hg to preserve tracheal mucosa blood flow and prevent erosion of the tracheal wall. Janson and Poulton<sup>21</sup> have demonstrated in an adult trachea model a 55 per cent incidence of seepage around the endotracheal tube cuff. When 5 cm H<sub>2</sub>O PEEP was applied, the seepage rate was reduced to 15 per cent. Many ICU physicians have used 5 cm H<sub>2</sub>O PEEP routinely to maintain functional residual capacity (FRC) in intubated patients. A secondary benefit of this treatment may be a reduction in hospital-acquired pneumonias.

Janson and Poulton also demonstrated 100 per cent seepage in all spontaneously breathing intubated patients even if PEEP was used. Clearly some additional prophylactic technique is needed to reduce the incidence of hospital-acquired pneumonia in intubated patients. Stoutenbeek et al<sup>40-42</sup> have demonstrated a significant reduction in hospital-acquired pneumonia by the decontamination of the oropharynx and gastrointestinal tract with topical nonabsorbable antibiotics. This combined with routine use of low level PEEP may be helpful in preventing hospital-acquired pneumonia in ventilated ICU patients.

A further reduction in hospital-acquired pneumonias is going to require a more detailed understanding of the pathophysiology. Overgrowth of bacteria in the stomach with reflux into the pharynx and colonization of oropharyngeal secretions does not appear to be the only mechanism of lung inoculation. Niederman et al<sup>32</sup> demonstrated *Pseudomonas* species in the lower airway but could not reliably demonstrate *Pseudomonas* species in the oropharyngeal area. Likewise Garvey et al<sup>16</sup> noted no subsequent colonization of nasogastric material when the lung was colonized or infected with gram-negative organisms. In both studies the proposed pathway of organisms from stomach to esophagus to oropharynx to trachea to lung could not be demonstrated. It appears that there are other, unidentified mechanisms leading to exogenous pulmonary inoculation. Prevention will be most difficult until this issue is clarified.

## DIAGNOSIS OF HOSPITAL-ACQUIRED PNEUMONIA

The usual diagnosis of a hospital-acquired pneumonia is based on fever, leukocytosis, purulent secretions, a new infiltrate on chest

roentgenogram, and the presence of bacteria in airway secretions.<sup>20</sup> In the patient on life support systems for several days, these criteria can be most difficult to interpret. Fever and leukocytosis can originate from another infected site such as urinary tract. Purulent sputum with bacteria can be from bronchitis with colonization of the trachea. Lung infiltrates on chest roentgenogram are difficult to distinguish from areas of atelectasis and edema. Routine upper airway suctioning in the intubated patient can be misleading, yielding a polymicrobial culture that is difficult to interpret and more difficult to treat. Use of antibiotics prematurely can be detrimental because it may result in the overgrowth of resistant organisms. There is a clear need to make an accurate diagnosis of colonization of the airway versus lung infection identifying the specific responsible organism with appropriate antibiotic sensitivity testing.<sup>1</sup>

Two techniques have been proposed to make an accurate bacteriologic diagnosis. The first is the use of a protected specimen brush.<sup>47</sup> During bronchoscopy of the suspected site identified on roentgenogram, a catheter is threaded into the lung through the bronchoscope. A sterile protected brush can then be advanced from inside the catheter and cross the suspected area of lung infection to collect a bacterial sample. The brush is then withdrawn from the bronchoscope and brushings cultured by standard techniques. Some evidence suggests that this approach separates routine upper airway flora associated with colonization from lower airway bacteria-producing pneumonia.

An alternative sampling technique is bronchoalveolar lavage with a fiberoptic bronchoscope placed in the area of lung infection.<sup>3</sup> Collection of airway washings from this area may improve the accuracy of bacteriologic diagnosis.

## ANTIBIOTIC THERAPY

Appropriate choice of antibiotics in patients with hospital-acquired pneumonia requires an understanding of the most likely flora in each clinical situation. Initial treatment can be empiric until culture results and antibiotic sensitivities are available. If the patient is intubated and ventilated and has been colonized with aerobic gram-negative rods, a third generation cephalosporin would be appropriate initial therapy. Ceftazidime is a good choice. However, if the patient is known to be colonized with *Pseudomonas* species, monotherapy may be inadequate. In this situation a third generation cephalosporin such as ceftazidime should be given with an aminoglycoside such as gentamicin or tobramycin. Finally gram-positive infection should be considered if *Staphylococcus* has been cultured from some site in the patient. Possible coverage for gram-positive pneumonia might include ticarcillin-clavulante or ampicillin-sulbactam.<sup>33</sup>

## SUMMARY

Nosocomial pneumonia represents a diagnostic, therapeutic, and prophylactic dilemma to the ICU physician. An episode of hospital-acquired pneumonia doubles or triples ICU length of stay, mortality, and cost. In today's cost-conscious medical environment, that is a grave consequence. Much work must be done to define mechanisms of lung infection in the ICU so that we can institute better prophylactic and therapeutic regimens. New approaches must be examined carefully to assure that an old complication is not exchanged for a new and more serious problem. Extensive use of systemic broad spectrum antibiotics to prevent nosocomial pneumonia may lead to a far worse problem by creating resistant organisms. Lung infections may be prevented if there is a better understanding of the mechanisms of pulmonary infections in critically ill patients.

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## **Immunologic Changes in Critically Ill Patients After Anesthesia and Surgery**

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It has been clear for many years that major infections are common and contribute greatly to morbidity after trauma and surgery.<sup>26, 39, 55</sup> Many factors are involved, however, and any examination of the problems of infection and its treatment must eventually come to the question of why the immunologic host defense mechanisms of traumatized patients are often impaired, leaving them more susceptible to infectious processes.

As an example, in our institution, 2 to 4 per cent of patients develop serious infections after open heart surgery, now one of the commonest operations in North America, and a procedure known to be associated with major impairment of host defenses.<sup>63</sup> These patients incur hospital costs that are five times greater than those having an uneventful recovery and account for nearly 15 per cent of hospital costs. Similar results, with a doubling of costs, have been reported by Nelson.<sup>47</sup> Extrapolation of this experience to the approximately 300,000 patients<sup>12</sup> undergoing open heart surgery in the United States in 1987 would lead to estimates of \$750 million as the cost of infections in this patient group alone. The economic and therapeutic implications for our patients from any increase in our knowledge are obvious.

The recent expansion of knowledge in the field of immunology requires that any examination of the response of the body to the noxious stimuli of anesthesia and surgery be undertaken from the broadest possible viewpoint. The immunologic responses that mobilize host defenses in response to anesthesia and surgery are complex and from an evolutionary standpoint are likely to be of value to the organism. As an example, interleukin-1 (IL-1), one of the first messengers involved in the activation of host defenses, has been identified in many primitive species.<sup>1</sup>

The immune system normally responds to incursions of foreign

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organisms, infectious processes generated by the body's own organisms, inflammatory processes of tissue injury, and processes specifically mediated by immune mechanisms, for example, anaphylaxis. These stimuli represent immunologic insults to which many systems in the body respond in attempt to protect the host. The components of this immunologic response are both specific and nonspecific and may be further subdivided into both humoral and cellular responses.

One of the principal components of this process is the lymphokine messenger compound IL-1. These immunologic insults cause IL-1 to be secreted by macrophages. As a messenger, IL-1 then initiates an interactive series of metabolic, endocrine, neurologic, and immunologic changes collectively termed the acute phase response. These interactions further involve immunoglobulins, the complement cascade, products of arachidonic acid (and cell membrane) reactions, and both the proteins and cells of the iron transport system.

Under normal circumstances the body has a spectrum of general or tissue host defenses. The skin, and the epithelial lining of the respiratory system and gastrointestinal and genitourinary tracts, with their mucous layers and fixed macrophages, allow man to coexist with the normal bacterial milieu and resist invasion by pathogens. The first line of resistance in these areas is conferred by the elaboration of secretory IgA in the respiratory tract, an acid milieu in the stomach and vagina, and mechanisms that prevent iron from existing in free form in the body.

## HUMORAL COMPONENT OF HOST DEFENSES

The host's humoral defenses that are breached by anesthesia and surgery include immunoglobulins; complement cascade and opsonins, for example, fibronectin; metabolites of arachidonic acid, for example, lysozymes; iron and iron transport proteins; and interleukins.

### Immunoglobulins

The immunoglobulins, IgG, IgA, IgM, IgD, and IgE, are proteins whose peptide chains are linked by disulphide bridges and which may be cleaved into antigen-binding (Fab) and Fc (originally, rabbit crystalline) fragments (Fig. 1).<sup>71</sup> The Fc fragments are responsible for the other, nonantibody activities of the molecule, for example, complement activation. The immunoglobulins are found in monomeric, dimeric, and polymeric forms. (Fig. 2).

IgG is comprised of four fractions, IgG 1 to 4. They have been termed the most important of the immunoglobulins and appear to contribute the most to antibody activity. In addition, they combine with complement to activate its cascade, and presumably acting as a messenger, become bound to lymphocytes, polymorphs, and macrophages.

IgA is largely found in the secretions of mucous membranes and contributes to the ability of the membrane to resist bacterial and viral

Figure 1. Four-chain structure of IgG. Inter-chain and intra-chain disulphide bridges are shown. Fragments from papain digestion, two Fab and one Fc fragment, include the antigen-bonding sites and the whole molecule 'membrane' and complement-binding sites. (From Humoral effectors of immunity. In Watkins J, Salo M (eds): Trauma, Stress and Immunity in Anaesthesia and Surgery. London, Butterworths, 1982, pp 13-14; with permission.)

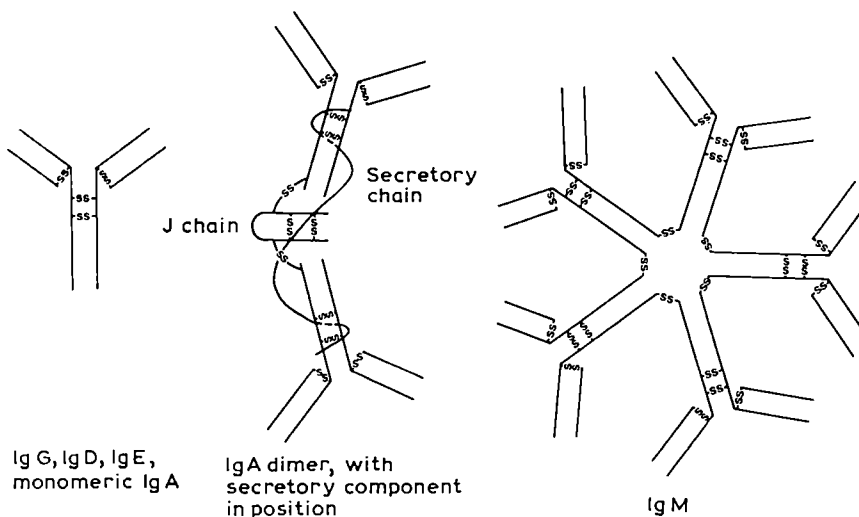
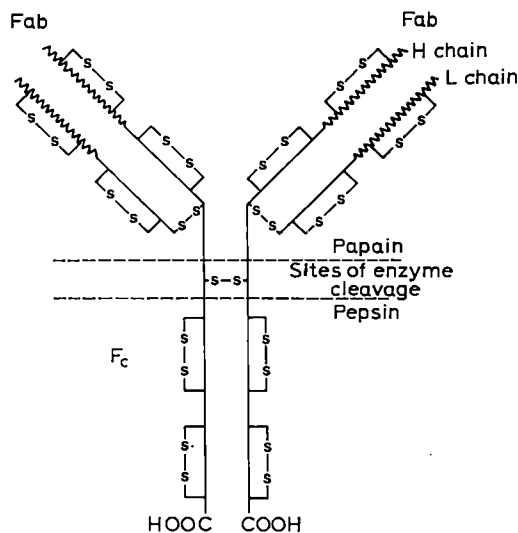


Figure 2. Structures of the five classes of immunoglobulin showing polymerization via J chains and disulphide bridges. (From Humoral effectors of immunity. In Watkins J and Salo M (eds): Trauma, Stress and Immunity in Anaesthesia and Surgery. London, Butterworths, 1982, 13-14; with permission.)

invasion. It is also thought to intercept antigenic material in foods that might otherwise induce autoimmune reactions.

IgM, the largest molecule of the group, possesses the most binding sites, five in number, and is the most efficient in terms of complement binding and agglutination.

IgD exists in very small amounts and has features in common with the more primitive immunoglobulins as well as IgE.

IgD and IgE antibodies are often associated with anaphylactic responses rather than infections and may mediate immunity to intestinal and other parasites.<sup>37</sup> They are beyond the scope of this review.

### **The Complement Cascade**

This system consists of nine major proteins, C1 to 9, with their corresponding activator and inhibitor proteins. Upon stimulation, these major proteins are converted to active enzymes, which then act serially on the next level of the cascade. Finally, after activation by the C4-C2-C3b complex, the final stage, the C5-9 "attack" complex is formed. This latter has the capacity for chemotactic and opsonic stimulation, activation of phagocytic cells, and target cell lysis. The complement system may be activated in two ways: (1) The classical pathway requires the reaction of an antigen-antibody complex. This interaction then leads to the exposure of a reactive site on the complex, which then activates C1. (2) In the alternate pathway, antibody is not required. The cascade is activated at C3 in the presence of a protein cofactor, properdin. This may occur with a number of substances, for example, endotoxin, dextran, Cremophor (Althesin), and some roentgenogram contrast media.

Complement activation facilitates phagocytosis and interacts with the coagulation and fibrinolytic cascades with prostaglandins, and does so synergistically to support defense of the host. However, under some circumstances harm rather than defense of the host may result. Widespread damage to the integrity of cell membranes from this process is common after open heart surgery, sepsis, and pancreatitis, and may be associated with clinical problems such as pulmonary dysfunction.<sup>9, 64, 72</sup>

### **Arachidonic Acid Derivatives**

The prostaglandins and leukotrienes are important mediators of the inflammatory response that regulate platelet activation, tissue permeability, and polymorphonuclear leukocytes.<sup>23</sup> Although often important in critical illness, their relationship is often indirect and is beyond the scope of this review.

### **Iron and Its Transport Proteins**

The acute phase response includes changes in plasma iron, transferrin (iron-binding capacity), lactoferrin, and ferritin. Further, iron and its transport proteins are of fundamental importance to any consideration of the relationship of immunologic mechanisms to infections since free iron is a facultative requirement for the growth of all

organisms<sup>11, 59, 73, 74</sup> and for the replication of many cell populations, particularly those involved in host defenses.<sup>20</sup>

Iron is transported to these cells bound to transferrin, which becomes complexed to transferrin receptors. Iron must also stay tightly bound in order to keep it inaccessible to micro-organisms. It is therefore telologically not surprising that transferrin receptors are widely present on the surface of many, perhaps all mammalian cells,<sup>10</sup> particularly those undergoing active replication, and certainly those involved in the maintenance of host defenses. The transported iron appears to be important for rapid cell growth and to be involved in the regulation of the genes essential to immune functions.<sup>46</sup> For example, iron and its transport proteins are important factors in the modulation of T-lymphocyte marker expression central to T-cell antigen recognition and activation.<sup>46, 48</sup>

Iron is not normally free in the body, but is tightly bound intracellularly to ferritin and lactotransferrin, and extracellularly in plasma to transferrin.<sup>5, 11</sup> With IL-1 secretion, serum iron levels and saturation of iron-binding capacity fall, and plasma lactotransferrin and ferritin levels rise. These changes make iron less available for bacterial growth.<sup>16, 21-23</sup> In an investigation of patients with acute infections, Baynes et al<sup>7</sup> described rising white blood cell counts and white blood cell and plasma lactotransferrin levels in survivors of lobar pneumonia compared with decreases in lactotransferrin levels in the nonsurvivors. Other studies have shown decreased white blood cell bacteriocidal capacity in the presence of reduced levels of intracellular lactotransferrin.<sup>27, 33, 41, 70</sup>

Similarly, iron precursors are normally not found free in the circulation. Hemoglobin released into plasma after lysis of red cells is rapidly bound to haptoglobin and thus is unavailable to micro-organisms. Saturation of iron-binding capacity is normally less than 35 per cent. At this level iron is essentially unavailable, and bacterial growth is inhibited. At higher levels, brought about by excessive amounts of iron or inadequate amounts of transferrin and other iron transport proteins, organisms can take iron from the iron-transferrin complex, and growth is facilitated.<sup>11, 73, 74</sup> This situation is seen commonly with severe infections or malignancies and occurs in a number of surgical settings, notably after open heart surgery.

Iron freed by the destruction of bacteria or cells of normal tissue is immediately bound to intracellular lactotransferrin, which is contained in white blood cells and macrophages.<sup>5, 7, 61, 70</sup> This process is facilitated by the presence of IL-1 secreted by macrophages. Similarly, extravascular blood is hemolyzed and the free hemoglobin is complexed with haptoglobin, effectively ensuring the elimination of free hemoglobin<sup>18</sup> from the circulation. Thus, transferrin, lactotransferrin, and haptoglobin may be considered bacteriostatic compounds.

## CELLULAR COMPONENTS OF HOST DEFENSES

The behavior of the cellular components, the lymphocytes, white blood cells, monocytes, and macrophage cells, is mediated by a num-

ber of polypeptides, proteins, and iron, which function interactively with other humoral and cellular factors and with complement to modulate the acute phase response to trauma.<sup>32, 62</sup> These cells are the effector arm of the immune response.

### Macrophages and Interleukin-1

The macrophages of this system are the subject of a recent review.<sup>32</sup> They originate from the granulocyte-monocyte series in bone marrow where they differentiate to monocytes and are released into the circulation. After several days, they diffuse into tissues where they differentiate and survive for about 3 months. Monocytes are activated by lymphokines such as interferon-gamma, which is secreted by T-cells. Under some circumstances monocytes can be activated directly by other macrophages through pathways such as the endotoxin-induced release of cachectin/tumor necrosis factor. Thus, exposure to endotoxin can lead to some degree of macrophage self-activation.<sup>13, 52</sup> Activated macrophages demonstrate increased killing capacity and a heightened secretion of many substances.<sup>45</sup> Among these substances is one of the principal messenger lymphokines, IL-1, which activates many of our host defenses, and in so doing gives rise to a spectrum of local and general reactions collectively termed the acute phase response (Table 1).<sup>14</sup>

### Lymphocytes and Natural Killer Cells

Lymphocytes, fundamental components of the immune system, are also stimulated by IL-1, leading to the production of increased

Table 1. *Interleukin-1 Responses*

---

|                                               |
|-----------------------------------------------|
| CNS                                           |
| Hypothalamus, fever                           |
| General                                       |
| Sleep                                         |
| Endocrine                                     |
| Stress hormone secretion                      |
| Insulin, TSH                                  |
| Growth hormone                                |
| Cortisol                                      |
| Humoral                                       |
| Protein catabolism amino acid released        |
| Free iron reduced                             |
| Lactotransferrin mobilized                    |
| Acute phase proteins secreted                 |
| Complement activation                         |
| Cellular                                      |
| WBC marrow stimulated, Neutrophilia           |
| Activation, superoxides                       |
| Chemotaxis                                    |
| B-cells, antibody production                  |
| T-cells, lymphokines (IL-2)                   |
| Evolution helper, cytolytic, suppressor cells |
| Natural killer cells stimulated               |
| Fibroblast proliferation                      |

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**Table 2.** *IL-1 Production of Increased Numbers of Lymphocytes and Cytolytic Cells*


---

|                                             |
|---------------------------------------------|
| T-cells: thymus cells                       |
| Lymphokine mediators secreted, eg, IL-2     |
| Cytotoxic cell lines elaborated             |
| T-cell subtypes                             |
| T-helper/T4 lymphocytes                     |
| B-cell interactions for antibody production |
| T suppressor/okT8/T8 lymphocytes            |
| B-cell antibody output inhibited            |
| Cytotoxicity inhibited                      |
| T Effector cells                            |
| T-cytotoxic cells                           |
| B-cells                                     |
| Specific antibodies produced                |
| Killer cells                                |
| Natural killer cells                        |

---

numbers of the various types of lymphocytes and cytolytic cells (Table 2).<sup>3</sup>

Lymphokine stimulation of the monocyte-macrophage system and of white blood cells activates these cells and leads to the production of natural killer (NK) cells and activation of T- and B-lymphocytes. These activated T cells secrete a number of lymphokines, for example, IL-2 and interferons alpha, beta, and gamma. IL-2 then stimulates the growth of helper, suppressor, and cytolytic T-cell species.<sup>14</sup> Interferon increases the cytotoxicity of NK cells.<sup>69</sup> The phagocytic activity that follows (that is, chemotaxis, opsonification, and superoxide generation) is mediated, at least in part by complement (C3), the Fc portion of IgG, iron, transferrin, and the opsonic glycoprotein, fibronectin. Without doubt other modulators remain to be discovered.

### Generalized Effects of Interleukin-1 Secretion

These stimuli produce an acute level of catabolic activity, with an initially high rate of loss of lean body mass and a rapid production of proteins that are metabolized in the liver. Teliologically this would not seem to possess great survival value because much of the resultant metabolic activity produces only energy, doing so in a wasteful and inefficient fashion. Nevertheless, the mechanism persists in almost all species and must be presumed beneficial. The usefulness may relate to the fact that a large fraction of this mobilized protein is used for the production of white blood cells, lymphocytes, and macrophages. Another portion is used for the production of large amounts of acute phase proteins by the liver in response to IL-1. The specific immunologic reasons for this are not entirely clear: but C-reactive protein may be required for opsonification of bacteria, and ceruloplasmin for free radical scavenging.

The effects on the central nervous and endocrine systems (drowsiness, depression of thyroid function, and secretion of ACTH, growth

hormone, sterols, and catechols) appear to be of more value to the organism. Lymphocytes and NK cells have receptors for enkephalins, opioid peptides, and cytokine thymosins. Recent evidence suggests that these compounds may represent neuroendocrine signals also capable of modulating immune responses peripherally, that is, the opioids and enkephalins may be the other, the central nervous system side of a closed loop.<sup>8, 19, 42</sup>

The role of the other proteins normally present in blood and those elicited by IL-1 stimulation leading to the acute phase response is less clear.

## EFFECTS OF ANESTHESIA AND OPERATION

It has been known for many years that severe compromise of the immune mechanisms occurs in patients in association with hemolysis, hemorrhage, burns, and chronic infections.<sup>2, 17, 26, 38, 39, 55, 63</sup> When Lassen and his associates<sup>36</sup> discovered that the prolonged administration of nitrous oxide could lead to leukopenia, others realized that many anesthetic drugs might impair immune competence. For anesthesia personnel, there appears to be no effects from exposure to trace levels of anesthetics in the usual clinical circumstances.<sup>58</sup> However, in healthy patients, some degree of immunosuppression occurs, even after the most uneventful anesthetic and surgical procedures.<sup>60</sup>

The ability of the anesthetic drugs to depress immune mechanisms has been the subject of many studies<sup>44, 49</sup> and reviews.<sup>30, 43</sup> In a group of normal kidney donors studied by Slade and his associates,<sup>60</sup> depression of almost all immune functions began with the induction of anesthesia and persisted for 24 to 36 hours. Lymphocyte reactivity began to recover by the second postoperative day, but recall antigen testing was depressed for many days after the operation.

The drugs commonly used for premedication, such as the benzodiazepines, narcotics,<sup>57</sup> and ketamine,<sup>53</sup> have minimal effects on immune function. In another study of a group of older patients undergoing hip replacement, NK cell activity was actually increased slightly following premedication.<sup>67</sup>

Moudgil reported a reduction of *in vitro* phagocytic activity of leukocytes exposed to the induction drugs thiopental, ketamine, and althesin, to a number of regional anesthetic agents, and to morphine and meperidine.<sup>44</sup> In other studies, Hammer demonstrated a dose-dependent reduction in metabolic activity of leukocytes exposed to lidocaine<sup>25</sup>. Thiopental was found to reduce chemiluminescence and neutrophil migration,<sup>34</sup> and halothane was shown to reduce bactericidal capacity of lung tissue.<sup>40</sup>

In normal healthy volunteers not undergoing surgery, Duncan et al<sup>16</sup> found that halothane and ethrane in oxygen given for 5 to 7 hours failed to effect lymphocyte transformation. Similarly, impaired responsiveness to PHA and concavalin A was noted in a group of patients who were studied after about 1 hour of balanced anesthesia with thio-

pental, N<sub>2</sub>O, O<sub>2</sub>, droperidol, fentanyl, and a relaxant.<sup>56</sup> However, some degree of depression of lymphocyte responsiveness occurred in another volunteer study of thiopental, halothane, N<sub>2</sub>O, and oxygen.<sup>15</sup>

The effects of anesthesia in the clinical setting are more difficult to assess. One must first take into account the immunologic changes brought about both by disease,<sup>22, 24</sup> intraoperative events such as blood transfusion and hypothermia,<sup>4</sup> and with the changes brought about by surgical trauma.

The immunologic status quo has been found to be less disturbed by regional than general anesthesia.<sup>54, 66, 68</sup> Hole<sup>29</sup> reported moderate depression of monocyte but not lymphocyte function assessed by *in vitro* thymidine uptake, but no changes with narcotics, diazepam, or bupivacaine. These activities could be potentiated by concomitant exposure to cortisol and prostaglandin-E<sub>2</sub>, suggesting a possible supplementary role for endocrine and other factors in the body's response to stress.<sup>6, 21, 28, 31</sup> Endocrine influences were thought to have contributed to the rapid recovery of NK-cell activity in patients who received epidural anesthesia in contrast to those given general anesthesia for upper abdominal surgery.<sup>66</sup> Epidural anesthesia appeared to be equally free of stress in a group of healthy parturients who showed NK-cell function to be better preserved postoperatively after epidural when compared with general anesthesia.<sup>54</sup> Similar findings were demonstrated in a group of patients having general or epidural anesthesia for hysterectomy.<sup>68</sup> Additionally, leukocytosis and decreased numbers of T- and B-lymphocytes occurred after general but not epidural anesthesia.

With general anesthesia, decreased levels of oxidative activity of white blood cells have been shown to occur *in vitro* with thiopental<sup>67</sup> and in patients undergoing general anesthesia for relatively short ear, nose, and throat procedures with halothane and enflurane.<sup>6</sup> However, 90 minutes after emergence, these functions had recovered to levels slightly above those at induction. Halothane has also been shown to produce a dose-dependent depression of activity of NK cells.<sup>24</sup> Lymphocyte reactivity is depressed after cholecystectomy and requires up to 3 days to recover to a normal level.<sup>66</sup>

The exposure of reasonably normal patients to anesthesia, under most circumstances, appears to be a minimal and readily reversible immunologic insult. Open heart surgery, now one of the commonest of operations, remains an exception to this rule. Surgery employing cardiopulmonary bypass has for many years been known to be followed by severe and protracted immune compromise.<sup>35, 50, 51, 63, 65</sup> Bypass with hemodilution and the use of intraoperative blood scavenging apparatus is associated with: (1) a 40 to 50 per cent reduction in the serum protein concentrations (immunoglobulins, transferrin, fibronectin and proteins of the complement cascade) persisting for 3 or 4 days in those patients with uncomplicated recoveries; (2) a high incidence of anergy at 48 hours<sup>75, 76</sup>; and (3) alterations in cellular host defenses, with decreased NK-cell activity, lymphocyte transformation, and lymphopenia. These changes were not affected by oxygenator

type or preoperative nutritional status. However, the risk of infection was greater in patients demonstrating a diminished preoperative response to antigen skin testing.

## SUMMARY

Host defenses and immune competence are to some degree impaired in all patients by disease and the events of anesthesia and surgery. The effects of anesthesia per se are usually small in comparison, but are not without consequence, particularly for critically ill patients. It is hoped that heightened awareness combined with greater knowledge of these problems will improve our patients' outcomes.

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## **Infections Acquired Through Blood Transfusion**

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Approximately 18 million blood components are transfused annually. Many of these are transfused during surgery and in the immediate postoperative period, times when the anesthesiologist is responsible for transfusion therapy decisions. The primary physician should discuss possible adverse effects of blood transfusion with the patient before surgery in order to obtain informed consent for use of these products. However, patients may expect to discuss the subject when the anesthesia team makes preoperative rounds. The primary physician should also ensure that the blood bank has orders for the type of blood products each patient needs. However, the anesthesiologist needs to assess the transfusion history and immune status of patients so that appropriate blood product orders are placed for special categories of patients such as neonates, patients with congenital clotting deficiencies, and transplant recipients. The physician who makes transfusion therapy decisions has little control over the safety of the blood products he administers and must depend on blood collection agencies to implement procedures that ensure that the safest possible blood is available for transfusion.

### **GENERAL DONOR SCREENING PROCEDURES**

Donor screening procedures employed by blood collection facilities are dictated by federal regulations<sup>40</sup> and standards established by voluntary accrediting organizations such as the American Association of Blood Banks<sup>142</sup> and the College of American Pathologists. In addition, large organizations such as the American Red Cross may have internal guidelines that elaborate on or exceed federal and voluntary standards.

There are three aspects to the donor screening procedure. The

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first is the donor history. This includes questions about current state of health, recent and remote illnesses, previous surgery, transfusion, jaundice, sexual habits, intravenous drug abuse, participation in or exposure to high-risk behavior,<sup>159</sup> and occupational and travel history. In addition to providing written information on high-risk behavior, the interviewer taking the history must discuss high-risk behavior to ensure that the donor has understood all questions. If all history questions are answered satisfactorily, a hemoglobin determination is made and a limited physical examination performed.

The examination includes temperature, pulse, blood pressure, inspection of general appearance, weight, and examination of exposed skin with special attention to the area to be used for blood donation. If the examination is also satisfactory, phlebotomy is performed. Since 1987, federal regulations have required a confidential unit exclusion policy whereby blood donors can indicate that their blood should not be used for transfusion but should be made available for research or other purposes. Several studies have evaluated the effectiveness of this policy and have provided evidence that high-risk donors have continued to donate blood,<sup>76, 112, 139</sup> perhaps to obtain testing for human immunodeficiency virus infection. If the donor indicates that the blood should be used for transfusion or does not provide any information, the unit is sent for routine serologic testing.

Donor blood is tested for ABO and Rh type, antibodies to red cell antigens (which may have been induced by previous pregnancy or blood transfusion), and infectious diseases transmitted by blood, which represent a health hazard to the transfusion recipient. In the United States, the routine tests for infectious diseases include a serologic test for syphilis, test for hepatitis B surface antigen (HBsAg), tests for antibodies to hepatitis B core antigen (anti-HBc), human immunodeficiency virus type I (HIV-I), and human T-cell leukemia/lymphoma virus type I/II (HTLV I/II), and serum alanine aminotransferase level (ALT). Some units will be screened for antibodies to cytomegalovirus (CMV). Outside the United States, tests for malaria and Chagas' disease may also be performed. When the donor has been determined to be negative for the serologic tests and to have a normal ALT level, the blood components from the donated unit are made available for transfusion. Despite this rigorous screening process, infections continue to be transmitted by transfusion. Subsequent sections of this article deal with the infections that occur and general measures that the physician can take to minimize the risk of transfusion-transmitted disease.

## HEPATITIS VIRUSES

Several viral agents have been demonstrated to cause post-transfusion hepatitis. These include CMV, Epstein-Barr virus (EBV), type A hepatitis virus (HAV), type B hepatitis virus (HBV), hepatitis delta virus (HDV), and the commonest form of post-transfusion hepatitis,

non-A, non-B (NANB) hepatitis. The diagnosis of NANB hepatitis is made based on the failure of patients' sera to react with viral agents known to cause hepatitis. Only rarely does HAV cause transfusion-transmitted hepatitis because there is not an asymptomatic carrier state.<sup>87</sup> EBV infections transmitted by transfusion are also rare. However, transfusion-transmitted infections with the other viral agents are not uncommon.

A recent article by Seef<sup>135</sup> presents the history of transfusion-transmitted hepatitis from the initial recognition of postinoculation jaundice in 1885 to the modern era. The modern era in post-transfusion hepatitis began with the identification of the Australian antigen and its association with hepatitis B infection. With the recognition of an infectious agent associated with type B hepatitis virus, specific tests were developed to identify the virus in blood donors.

In the 1970s several studies of post-transfusion hepatitis revealed attack rates of 6 to 45 per cent, with the highest rates being in recipients of commercial blood. Serologic studies revealed that 63 to 88 per cent of the cases of post-transfusion hepatitis were not caused by known viral agents. These studies are summarized in a classic review by Aach and Kahn.<sup>1</sup> Other important observations made during this era include (1) a reduction in type B hepatitis following the implementation of HBsAg testing; (2) a strong association between use of commercial blood donors and high prevalence rates of post-transfusion hepatitis; and (3) an association between elevated donor alanine aminotransferase levels and the ability of a unit to transmit post-transfusion hepatitis.<sup>2</sup>

There are no recent studies of post-transfusion hepatitis in the United States. However, a study from Toronto<sup>56</sup> conducted between 1983 and 1985 demonstrated an attack rate of 9.2 per cent with all patients having NANB hepatitis. Surrogate testing for NANB hepatitis has not been instituted in Canada because epidemiologic studies in that population indicate that it would not be an effective preventive measure. Recent studies in France<sup>14</sup> and Italy<sup>41, 152</sup> reported post-transfusion hepatitis rates of 7.1 and 14.2 per cent in cardiac surgery patients. In Italy, where there is a higher endemic rate of hepatitis, 96 per cent of the patients had NANB hepatitis, 3 per cent type B hepatitis, and 1 per cent CMV hepatitis. These studies support a post-transfusion hepatitis rate of 7 to 15 per cent in patients prior to the institution of surrogate screening.

### Type B Hepatitis

The hepatitis B virus is one of the most important human pathogens, causing over 300 million cases of chronic infection in the world. It is estimated that approximately 50 per cent of those infected will die of HBV-related causes.<sup>118, 135</sup>

The molecular analysis of hepatitis B virus and hepatitis B virus infections has recently been reviewed<sup>118</sup> and is covered in another article in this issue. There are three antigen complexes associated with infection by hepatitis B virus. The outer viral coat is recognized as

hepatitis B surface antigen (HBsAg). The inner nuclear capsid protein is recognized as core antigen (HBcAg). One other viral antigen, the e antigen (HBeAg), can also be detected. Certain forms of the surface antigen and e antigen are indicative of viral infection but are not infectious. HBeAg occurs as a free protein in serum. Recent studies by Miller<sup>99</sup> indicate that serum e antigen is generated from the hepatitis B virus core protein. When hepatitis B virus infection occurs, the liver and peripheral blood lymphocytes appear to be infected with virus.<sup>118</sup>

The first detectable serum marker of hepatitis B virus infection is HBsAg. Six weeks to 3 months after the detection of HBsAg, antibody to the core protein (anti-HBc) becomes detectable followed by anti-HBs if there is resolution of the acute infection. Over time, anti-HBc may decrease in titer, but anti-HBs persists. In individuals who become chronically infected with the virus, HBsAg and anti-HBc remain detectable. HBeAg is usually detectable for 2 to 8 weeks after infection. However, in individuals who are chronically infected with hepatitis B virus, the e antigen may be detectable for long periods of time. The hepatitis B virus genome has been detected in liver tissue and lymphoid cells of individuals who do not have serologic markers of hepatitis B infection.<sup>10, 83, 118</sup>

Seef has estimated that not more than 25 per cent of cases of post-transfusion hepatitis were ever caused by the type B hepatitis virus.<sup>135</sup> In nonendemic areas of the world, type B hepatitis accounts for less than 10 per cent of cases<sup>1, 14, 56, 81</sup> and in many studies, hepatitis B infection causes fewer than 3 per cent of cases of post-transfusion hepatitis. Experts believe that a small number of cases originally classified as NANB are infections with HBV in which the virus is an HBV variant or the host does not have serologic markers of HBV infection.<sup>10, 81, 96, 135, 144, 164</sup>

### Problems in Donor Screening

The development of type B hepatitis (or seroconversion to type B hepatitis) in patients with hemophilia A and hemophilia B who received clotting concentrates produced from seronegative plasma indicates that the current screening tests for type B hepatitis are not sufficiently sensitive.<sup>135</sup> Studies in chimpanzees have demonstrated that reactive sera diluted below the level of positivity in the radioimmunoassay can transmit type B hepatitis to chimpanzees. Molecular biology techniques using hepatitis B virus DNA probes have demonstrated that a small number of blood donors may carry the hepatitis B virus genome in their lymphocytes, yet have no evidence of serologic infection with hepatitis B virus.

Studies in Sardinia,<sup>83</sup> an area endemic for hepatitis B, have shown that hepatitis B virus DNA was detected by dot blot hybridization in blood donors who were negative for HBsAg. When these individuals were divided into groups that had abnormal and normal ALT levels, 9 per cent with elevated ALT were HBV-DNA positive, whereas only 0.5 per cent of those with normal ALT levels were HBV-DNA positive. The most disturbing aspect of this particular study is that 69 per cent

of the individuals who had HBV DNA in their serum were negative for all serologic markers of HBV infection. These results are not readily translated to areas in which HBV is not endemic. Studies performed in France<sup>59</sup> investigated HBV DNA in the serum of a thousand units of blood collected from volunteer donors. No serum positive for HBV DNA and negative for HBsAg was found.

### **Delta Hepatitis Virus**

Hepatitis delta virus (HDV) is a defective RNA virus that only infects individuals already infected with HBV. The biology of HDV has been recently reviewed.<sup>28, 107</sup> The average transfusion recipient is not at risk for HDV infection because most individuals are not HBV carriers. However, the risk of HDV is a particular problem for patients with hemophilia, many of whom are infected with HBV. It is also a risk for multitransfused patients, such as patients with thalassemia and sickle cell anemia.

Transfusion-related HDV has been reviewed by Rizzetto and colleagues.<sup>125</sup> The prevalence of HDV in a multicenter study was 3.4 per cent. Inagaki et al<sup>73</sup> reported that the prevalence of HDV infection in Japanese hemophiliacs who had received imported clotting concentrates was 66.7 per cent, whereas the prevalence of HDV in carriers of type B hepatitis who did not receive such products was 0.9 per cent. This correlated with the frequency of antibodies to HIV. In Europe, the prevalence of antibodies to HDV in HBsAg-positive hemophiliacs treated with commercial products varied from 27 to 85 per cent, whereas none of the hemophiliacs positive for surface antigen treated with locally prepared coagulation factors appeared to be infected with HDV.<sup>125</sup> In normal donor populations, measures taken to eliminate HBV should also be effective in preventing HDV.

### **Non-A, Non-B Hepatitis**

NANB hepatitis accounts for 70 to 100 per cent of cases of post-transfusion hepatitis.<sup>1, 56, 152, 164</sup> Several articles have summarized the epidemiologic and experimental data that support a viral etiology of the disease and recent reports have indicated that the cDNA from a candidate virus has been cloned.<sup>10, 26, 34a, 48, 49, 50, 68, 145</sup> NANB hepatitis is the most important viral infection transmitted by blood transfusion because of the large number of individuals infected and the great potential for developing chronic disease. At a workshop sponsored by the Food and Drug Administration to review the status of surrogate testing, investigators from the Centers for Disease Control (CDC) presented data on the prevalence of post-transfusion NANB hepatitis and the potential consequences of this infection.<sup>170</sup> Data from four sentinel counties followed by the CDC indicated that NANB hepatitis represented 20 to 40 per cent of all acute viral hepatitis and that 16 to 24 per cent of these cases represented infections transmitted by transfusions. Using published reports of chronicity in NANB post-transfusion hepatitis (NANB-PTH), it was estimated that 48,000 patients develop acute NANB-PTH annually in the United States, and

that 24,000 of these develop chronic infections, with 2400 developing cirrhosis. Although the chronic liver disease caused by transfusion is believed to be small relative to that caused by drug abuse and other sources of infection,<sup>10</sup> transfusion-transmitted NANB hepatitis represents an important complication of blood transfusion.

In the United States, current donor screening procedures for NANB hepatitis include donor ALT levels and anti-HBc. Data from the 1970s suggested that units with elevated ALT levels transmitted hepatitis more frequently than units with normal ALT levels.<sup>1</sup> Some studies have confirmed this observation<sup>2, 165</sup> but others have not.<sup>30, 61</sup> Testing for anti-HBc has also yielded positive<sup>79, 81, 144</sup> and negative results.<sup>67, 77</sup>

The usefulness of surrogate testing of blood for transfusion depends on the characteristics of the donor population. Studies conducted by the American Red Cross indicate that elevated ALT levels vary from 1.7 to 5.6 per cent depending on donor's race, sex, and geographic location.<sup>136</sup> The prevalence of anti-HBc varies with geographic location, ranging from 0.55 to 6.38 per cent with an overall prevalence of 2.6 per cent.<sup>79</sup> Although blood centers in the United States have implemented ALT and anti-HBc testing, centers in Canada and the United Kingdom have not.

The arguments for surrogate testing and a summary of supporting studies are presented by Menitove.<sup>96</sup> Recent data from Germany,<sup>144</sup> where ALT levels have been used for donor screening for some time, indicated that hepatitis developed in 10.1 per cent of those receiving blood that was anti-HBc positive (with normal ALT levels) and in only 2.1 per cent of those who received anti-HBc negative blood. These studies support the institution of surrogate testing. Although data are not yet available from the United States, surrogate testing is expected to decrease the frequency of PTH by approximately 40 per cent.

A specific assay has now been developed for the blood-borne form of NANB.<sup>81a</sup> When this assay was used with seven human sera samples shown to transmit NANB to chimpanzees, six were positive for antibodies. The agent responsible for NANB hepatitis has been designated the hepatitis C virus (HCV). Antibody to HCV was found in all patients from a small series that developed chronic NANB hepatitis after transfusion.<sup>81a</sup> With the development of this specific test for HCV, there may soon be a clinical assay for screening blood to prevent post-transfusion NANB caused by this virus. Further research will be necessary to determine if there are additional agents responsible for post-transfusion NANB.

## HUMAN IMMUNODEFICIENCY VIRUSES

Human immunodeficiency viruses (HIV) are RNA retroviruses belonging to the nontransforming lentivirus family.<sup>54, 168</sup> To date two<sup>38, 39, 54, 70, 168</sup> and possibly three<sup>91</sup> distinct variants have been described. These viruses have a selective tropism for cells of the im-

mune and neurologic systems. They have been demonstrated to be the etiologic agents of the acquired immune deficiency syndrome (AIDS) and related disorders.<sup>38, 54, 70, 91, 168</sup> The molecular structure of HIV and the mechanisms of pathogenesis have been reviewed extensively elsewhere.<sup>54, 60, 126, 141, 168</sup> However, there are several aspects of HIV infection that are important in understanding problems associated with serologic tests used to screen blood donors. These will be reviewed briefly.

When an individual is infected initially with HIV, the virus binds to lymphocytes, monocytes, and some cells of the central nervous system (CNS). The CD4 molecule is the receptor for virus attachment and is expressed primarily on the T4 subset of lymphocytes (helper/inducer) and on some monocyte/macrophages. The virus is internalized and the viral RNA transcribed into DNA by viral reverse transcriptase. The proviral DNA is produced in large amounts. Some copies are integrated into host DNA and other copies remain free in the cell. The virus then replicates and disseminates to infect other cells. This initial phase of acute dissemination lasts for several weeks. The host may have a flu-like syndrome or be asymptomatic. At this stage, HIV may be recovered from plasma and cells, and viral antigens can be detected in plasma. Antibodies to HIV are not detectable at this time. As the host develops antibodies to the virus, viral replication subsides, and the infection enters a latent phase. The host is asymptomatic during the latent phase, but antibodies to a number of viral proteins may be detectable. The earliest antibodies are to core proteins (p24/25) and the most persistent antibodies are to the envelope proteins (gp41/42, gp120). Screening assays to identify HIV-infected blood donors are based on the detection of these antibodies.

### **Epidemiology of Transfusion-Transmitted Acquired Immunodeficiency Syndrome**

The first case of transfusion-transmitted AIDS (TTA) was reported in 1982 in an infant who underwent exchange transfusion for Rh hemolytic disease of the newborn.<sup>12</sup> Subsequent reports confirmed the ability of transfusion to transmit AIDS.<sup>18, 65, 110</sup> Surveys conducted by the CDC indicate that 2 per cent of AIDS cases are related to transfusion of single donor blood products and 1 per cent are in patients with hemophilia who received clotting concentrates.<sup>44, 71, 119</sup> As of February 20, 1989 the total number of cases of TTA reported to the CDC was 2362 (personal communication). Of these, 176 were in children and 2186 were in adults. Most of these cases were caused by blood transfused prior to March 1985, the date when serologic testing for HIV became available. However, HIV infection has been reported in individuals who were recipients of HIV seronegative blood.<sup>158</sup>

The incubation period of transfusion-transmitted AIDS depends on the recipient's age and immunologic status. Using as a data base 297 cases reported to CDC, Medley et al<sup>93</sup> calculated the incubation period for AIDS acquired via blood transfusion. The median incubation time for individuals less than 5 years of age was 1.90 years. For

recipients between the ages of 5 and 59, the incubation time was 7.97 years; this decreased to 5.44 years for patients 60 years and older. The incubation time for immunologically compromised patients appears to be shortened and closer to the times observed in infants and young children.<sup>130</sup> Reporting on a cluster of HIV cases in immunocompromised patients related to transfusion from a single donor, Anderson et al<sup>13</sup> reported the development of immunologic and clinical sequelae a median of 286 days after transfusion.

### Problems in Donor Screening

The donor history questions, which are designed to eliminate individuals who might transmit HIV infection, relate to signs and symptoms of AIDS, AIDS-related complex, and Kaposi's sarcoma. Specific questions are asked about intravenous drug abuse, male homosexual activity, contact with prostitutes, bisexuality, and other sexual practices. Also, individuals from areas endemic for HIV-1 and HIV-2 infection are permanently excluded from donating blood. Individuals who have received blood transfusions themselves within the preceding 6 months are temporarily deferred.

The initial screening test to detect antibodies to HIV in the United States is an enzyme-linked immunosorbent assay (ELISA), with the Western-blot test used for confirmation of positive assays. The frequency of persistently positive ELISA donors in the American Red Cross blood centers is 0.33 per cent.<sup>82</sup> The percentage of samples that are Western-blot positive is 0.031 per cent. Both assays may present problems in interpretation. These problems are presented and discussed in recent reports.<sup>33, 42, 122, 133</sup>

HIV infection has been transmitted by single donor blood products<sup>78, 158</sup> and by clotting concentrate made from the plasma of donors who tested negative for HIV antibodies.<sup>9, 74, 94, 128</sup> The frequency with which seronegative blood will transmit HIV infection is 1 to 3 cases per 100,000 transfusions.<sup>21, 52, 78, 95, 106, 109, 143, 157, 158</sup> Serologic testing for HIV antibodies will not eliminate donors in the "window period" between initial infection and the development of antibodies to HIV. Although this window period was thought to be 6 to 14 weeks,<sup>33, 58, 158</sup> a recent study by Farzadegan et al<sup>53</sup> suggests that seropositive asymptomatic homosexual men may lose antibodies to HIV without experiencing disease progression. Investigations of donors whose seronegative units transmitted AIDS have revealed that most of them belong to high-risk groups but they have not identified themselves as such.<sup>158</sup> Comparisons of serologic tests for donors who exercised the confidential unit exclusion option with serologic tests from other donors indicate that members of high-risk groups are continuing to donate blood.

Many local health departments have established alternative test sites for those seeking HIV testing, but test results are often not available for many weeks. The introduction of the rapid latex agglutination assay for HIV, which can be performed in several minutes, may have some impact on continued donation by high-risk donors.<sup>120</sup>

An alternative approach is to test blood donors for HIV antigens that may be detectable in infected individuals when antibody is absent.<sup>11, 24, 43, 55, 111</sup> The Food and Drug Administration (FDA) has been assessing data on the use of HIV antigen testing for donor screening. Current findings suggest that HIV antigen testing does not improve on HIV-antibody screening and may result in more false-positive results. The FDA evaluation concluded that blood should not be tested for HIV antigen at this time because it would not improve on current screening procedures.

Existing ELISA assays detect primarily HIV-1 infection and identify only 30 per cent or less of HIV-2 infections.<sup>137</sup> HIV-2 infection is not a serious concern in blood donors in the United States at this time,<sup>70</sup> but if this virus should spread to intravenous drug users, the need for specific serologic testing for HIV-2 may change.

### HUMAN T-CELL LEUKEMIA/LYMPHOMA VIRUSES TYPE I AND II

T-cell leukemia/lymphoma viruses (HTLV-I/II) are retroviruses that have the capacity to induce neoplastic transformation of the infected cell. HTLV-I has been demonstrated to be etiologically associated with adult T-cell leukemia<sup>86, 113, 140, 168</sup> and chronic progressive myelopathy, also called tropical spastic paraparesis.<sup>20, 29</sup> Recent studies indicate that the HTLV-I genome is also found in some patients with multiple sclerosis.<sup>123</sup> The virus is endemic in southeast Japan, the Caribbean basin, Central and South America, and Africa. Studies performed by the Japanese demonstrated that seropositive individuals are infectious and that blood transfusion can cause persistent infection.<sup>129</sup> The incubation period for HTLV-I related disease is long. For adult T-cell leukemia the incubation period may be 20 to 30 years, and no case related to blood transfusion has been documented. However, unpublished Japanese data suggest that chronic progressive myelopathy probably can be transmitted by transfusion with a mean incubation period estimated to be 4 years.

Donor screening in the United States began in January 1989. The screening tests, which have been approved for use by the FDA, are enzyme immunoassays. Because of crossreactivity between HTLV-I and HTLV-II a positive result in the screening test does not distinguish between the two viruses. Western immunoblot and radioimmuno-precipitation assays are used to confirm positive results but cannot be used to distinguish HTLV-I from HTLV-II infection. Studies performed by the Red Cross in eight blood centers located throughout the country indicate that 0.025 per cent of blood donors carry the virus.<sup>166</sup> Demographic studies of seropositive donors revealed that 6 of 7 seropositive donors were black and 4 of 7 seropositive donors admitted drug abuse or sexual contact with intravenous drug users. In this regard, data recently published in the *New York Times*<sup>80</sup> indicate that HTLV-II is found in 4 to 20 per cent of intravenous drug

users and in approximately 1 in 10,000 blood donors in San Francisco, Los Angeles, and New Orleans.

Studies in patients with hematologic diseases in the United States indicate that 2 to 3 per cent of such individuals are infected with HTLV-I.<sup>75, 100</sup> Studies in patients with hemophilia did not detect infected individuals, suggesting that the virus is always cell associated and transmitted by products containing lymphocytes.<sup>73</sup> Hemodialysis patients, another group of multiply transfused patients, have an increased prevalence of HTLV-I infection. Japanese investigators have reported the prevalence of HTLV-I infection in patients requiring hemodialysis to be 0 to 4.8 per cent in nonendemic areas and 9 to 18 per cent in endemic areas.<sup>103</sup>

Screening procedures to eliminate HTLV-I seropositive blood were begun in 1986 in endemic areas of Japan. Recently, Inaba and colleagues reported on the effectiveness of these measures.<sup>72</sup> Six hundred seventy-five recipients of blood found to be seronegative for HTLV-I using a passive agglutination assay were followed for 50 days after transfusion. One patient seroconverted (0.15 per cent) despite the use of screened blood. However, the seroconversion rate prior to screening was 8.3 per cent.

Clearly, donor screening reduces the risk of spreading HTLV-I through transfusion. It is too early to assess the impact of screening procedures on multiply transfused patients in the United States.

## CYTOMEGALOVIRUS INFECTIONS

CMVs are complex DNA viruses that are members of the herpes family. Human CMV is a very large virus with a molecular weight of 150,000 to 160,000 daltons. The organization of the CMV genome and its biology and replication have been reviewed extensively elsewhere.<sup>45, 84, 101, 108</sup> One of the characteristics of the herpes viruses is their ability to establish latent infections in the host following primary infection. Peripheral blood lymphocytes and monocytes can harbor latent virus.<sup>132</sup> Although the nature of latent infections is not understood, recent publications have described several factors that contribute to reactivation of CMV in the host.<sup>32, 36, 63, 108, 136</sup>

The prevalence of CMV infections is low in infancy but increases with age. In the elderly, virtually 100 per cent of individuals are infected.<sup>4, 5, 7, 8, 148, 149</sup> The prevalence of infection also varies with geographic location and socioeconomic level. Population studies of complement fixing antibodies to CMV among healthy blood donors in different parts of the world reveal that Western countries, such as France, have a 40 per cent seropositive rate, whereas in the Philippines the rate of seropositivity is 100 per cent.<sup>148</sup> Although most infections with CMV appear to be asymptomatic or associated with minimal symptomatology, congenital CMV infection and CMV infection in neonates and immunosuppressed patients are associated with significant morbidity and mortality.

Symptomatic CMV infections may be associated with primary infection, reactivation of a latent infection, or may represent reinfection with a new strain of CMV. Active infection is usually documented by virus isolation or the development of antibodies to cytomegalovirus.<sup>5, 8, 148</sup> Active CMV infection is associated with both IgM and IgG anti-CMV antibodies.<sup>148, 149</sup> Reactivation of a latent infection or reinfection with a different strain of CMV was difficult to document until recently. Now using molecular biology techniques that distinguish DNA restriction fragment polymorphisms, reactivation and reinfection can be distinguished.

### Transfusion-Transmitted Infections

CMV infection was first documented to be transmitted through blood transfusions in the late 1960s. Patients having open heart surgery were observed to develop fever, splenomegaly, and lymphocytosis postoperatively but were negative for heterophile antibodies. CMV was documented to be the etiologic agent of the syndrome called "post-perfusion syndrome" or "post-perfusion mononucleosis." Since the original descriptions, many studies of transfusion-transmitted CMV have been performed.<sup>5, 8, 148</sup>

Studies performed between 1968 and 1978 showed that the CMV seroconversion rate after transfusion in immunologically normal individuals varied from 9.7 to 58 per cent.<sup>5, 8, 114, 116, 148</sup> These studies used viral isolation or a fourfold increase in antibody titer in the complement fixation assay as the criteria for infection. Only a small percentage of the patients showing serologic evidence of CMV infection were symptomatic. Adler<sup>8</sup> summarized the data from several studies and expressed these data as number of patients seroconverted per 100 units of blood transfused. The seroconversion rate was 2.5 to 12 patients per 100 units of blood transfused. A more recent study performed between 1983 and 1985, a period when some of the donor screening procedures for AIDS were in place, reported that 0.9 per cent of 637 immunologically normal transfusion recipients developed CMV infection.<sup>115</sup> This represents a seroconversion rate of 0.14 per cent per unit transfused or 0.3 per cent per seropositive unit transfused.

There is no convincing evidence that CMV infections occurring in immunologically normal individuals cause long-term morbidity. However, CMV infections occurring in immunologically compromised recipients cause substantial morbidity and mortality.<sup>3, 4, 19, 22, 23, 35, 62, 151, 153, 161</sup> Several studies documented the development of disseminated CMV infection with hepatitis and coagulation abnormalities in low birth weight neonates who were transfused with CMV seropositive blood.<sup>4, 17</sup> Recipients of bone marrow transplants<sup>23, 97, 98, 156</sup> and of solid organ transplants<sup>19, 63, 121</sup> who are seronegative are also at risk of interstitial pneumonia when primary CMV infection occurs.

There are four types of individuals who have been identified as needing CMV seronegative blood: (1) neonates weighing less than

1200 g at birth when either the neonatal recipient or the mother is CMV-antibody negative or the information is unknown;<sup>150</sup> (2) transplant recipients who are seronegative and whose donors are also seronegative;<sup>23, 63, 121</sup> (3) seronegative pregnant women who require transfusion; and (4) seronegative patients undergoing splenectomy.<sup>5</sup>

CMV infections transmitted by blood transfusion are associated with the transfusion of cellular components of blood such as red cells, platelets, and granulocytes. Products such as fresh frozen plasma and cryoprecipitate appear to carry a very minimal risk of transmitting CMV. In the optimal setting, cellular blood products should be obtained from blood donors who are seronegative for antibody to CMV. When such products are not available, deglycerolized washed red cells,<sup>19, 27, 147</sup> but not liquid stored washed red cells,<sup>46, 88</sup> have been demonstrated to decrease the risk of transfusion-transmitted CMV. A new generation of filters designed to remove leucocytes from blood products may be useful for decreasing the risk of infection when using CMV seropositive donors.

### Problems with Donor Screening

Blood centers have provided CMV seronegative blood for neonatal transfusion on a routine basis for several years. There are several tests suitable for screening blood donors for antibodies to CMV. These assays include indirect hemagglutination, indirect fluorescence, enzyme immunoassays and passive latex agglutination tests.<sup>15, 37, 57, 146</sup> For blood centers performing batch testing of donors on an elective schedule either test appears satisfactory. However, for emergency screening, passive latex agglutination is faster and technically easier.<sup>25, 57</sup> The turn around time is also shorter. In general, the cost of the passive latex agglutination test is higher. The problem with providing seronegative blood for patient populations at risk stems from the relatively high prevalence of CMV seropositive normal adult donors.

Studies suggest that only 5 per cent of donors are actually capable of transmitting CMV.<sup>8, 148</sup> A number of investigators have studied donors for both IgM anti-CMV and IgG anti-CMV in an attempt to identify donors who are capable of transmitting infection. In most studies, donor blood that contained IgM anti-CMV was more likely to transmit infection than blood which contained only IgG anti-CMV.<sup>16, 85</sup> These results suggest that in geographic areas where 80 to 100 per cent of blood donors may be positive for CMV, selecting units that lack IgM anti-CMV may help provide suitable blood products.

### EPSTEIN-BARR VIRUS

Occasionally, the post-perfusion syndrome may occur without detectable antibodies to CMV. Epstein-Barr virus (EBV) has been demonstrated to be the etiologic agent in many of these cases. Henle and Henle<sup>69</sup> and McMonigal and colleagues<sup>92</sup> have reviewed the spectrum

of EBV illness transmitted by transfusion. Blood donations are not screened for antibodies to EBV because most adults are immune to the virus and are not susceptible to infection. Immunity to the virus is rare in infancy but by adulthood most individuals have been infected. Like the other herpes viruses, EBV remains in host cells in a latent form following primary infection. The EBV genome may be detected in B lymphocytes from asymptomatic seropositive donors. Over 90 per cent of blood donors have antibody to EBV. The virus infects donors and recipients with about the same frequency and thus transfusion-transmitted disease appears to be rare.

One might expect infants and children to be more susceptible because of the higher frequency of seronegative individuals in this age group. Henle and Henle<sup>69</sup> reported on studies conducted by Dr. Gary Fleisher at the Children's Hospital of Philadelphia in which 25 seronegative children who were transfused were followed for 6 to 12 months to determine the frequency of transfusion-transmitted EBV infection. In 23 of 25 patients, passively transferred antibodies to EBV were detected after transfusion. These antibodies disappeared during the follow-up period and in only 1 of 25 was there evidence of seroconversion. These results suggest that antibodies in the donor blood protect the recipient from developing EBV infection.

When EBV-related illness is transmitted by transfusion, symptoms typically begin 5 to 7 weeks post-transfusion but may occur earlier in splenectomized patients. Fever, malaise, and dark urine, accompanied by variable hepatomegaly and splenomegaly are the typical presenting symptoms. Pharyngitis and lymphadenopathy are not usually present. Serious morbidity may be observed in immunosuppressed patients. Overall, clinical disease caused by EBV transmitted by transfusion is considered to be a lesser problem than some of the other transfusion-transmitted infections.

## BACTERIAL INFECTIONS

Bacterial contamination of blood was not uncommon prior to the development of plastic bags that permit a closed system for blood collection and component preparation. Prior to 1975, federal regulations required that routine sterility testing be performed on outdated blood, but subsequently these requirements were eliminated. There are now occasional reports of sepsis following transfusion. Reviewing fatalities associated with blood transfusion reported to the FDA between April 3, 1976 and December 31, 1979, Myhre<sup>104, 105</sup> found that 2 of 77 fatalities could be attributed to bacterial contamination.

In a more recent paper, published reports of transfusion reactions caused by contaminated blood components are summarized.<sup>134</sup> *Pseudomonas fluorescens* is the organism most commonly isolated from cold-stored red cells. When bacteria are isolated from platelet concentrates they are usually gram-positive organisms, often staphylococcal species. Septicemia caused by transfusion of contaminated

blood products is frequently fatal, even when the nature of the reaction is promptly recognized and therapy instituted.

There are four ways in which bacterial contamination of blood components can occur: (1) the donor skin is inadequately prepared and the unit is contaminated at the time of phlebotomy; (2) the donor has an inapparent septicemia;<sup>169</sup> (3) the collecting bag or solution is not sterile; and (4) the sterility of the unit is violated when a component is made or the product is manipulated prior to infusion. In an original case report by Scott et al,<sup>134</sup> the implicated unit, which was contaminated with *Pseudomonas fluorescens*, may not have been properly stored at all times. It had been issued and returned to the blood bank three times prior to transfusion. Although there are no specific preventive steps to be taken at blood centers, the transfusion service and blood bank should carefully monitor the duration of time blood products are out of controlled refrigeration and rigidly adhere to all expiration times. Those involved in transfusion therapy should promptly return to the blood bank or a facility for proper storage all products that cannot be infused within 30 minutes of issuance and should complete all transfusions within 4 hours of entering the product.

### TREPONEMAL INFECTIONS

Syphilis transmitted by transfusion is another rare complication. A search of the literature failed to identify any reports in the English language after 1983. *Treponema pallidum* is killed by cold storage. Clinical case reports and laboratory studies suggest that the organism does not survive beyond 120 hours in blood components stored between 1 and 6 degrees centigrade.<sup>154, 155</sup> However, the organism can survive in platelets (which are stored at 22 degrees centigrade), and can be isolated from fresh blood.<sup>34</sup> The case reported in 1983 by Risseuw-Appel and Kothe<sup>124</sup> involved exchange transfusion with fresh heparinized whole blood from a seronegative donor who subsequently developed symptoms.

Federal regulations require that a serologic test for syphilis be performed. The American Association of Blood Banks dropped the requirement for such testing in 1978. In an international forum published in *Vox Sanguinis* in 1981,<sup>51</sup> experts in transfusion medicine expressed their views about screening of blood donors for syphilis. Three experts were from the United States. All of them thought the current screening tests that used cardiolipin antigen were ineffective. The tests were not sensitive enough to detect early infections and resulted in more biological false-positive reactions than cases of real infection. Four of six European experts favored maintaining testing but felt that a more specific test such as the *T pallidum* hemagglutination assay should be used.<sup>117</sup> One European expert was neutral, and the sixth expert thought that testing was ineffective. Federal authorities were considering removing the requirement for syphilis testing,

when the AIDS epidemic occurred. Since individuals with syphilis may engage in sexual practices that also make them at higher risk of HIV infection, syphilis testing may additionally help in protecting the blood supply from transfusion transmitted AIDS.

## PARASITIC DISEASES

### Malaria

Malaria attributable to blood transfusion is now an uncommon event in the United States. Guerrero and others<sup>66</sup> described 26 cases reported to the Centers for Disease Control between 1972 and 1981. Bruce-Chwatt<sup>162</sup> indicated that the World Health Organization received reports of 536 cases of transfusion malaria occurring in 35 countries between 1978 and 1982. Transfusion-transmitted malaria is thought to be under-reported.<sup>31</sup> There is the general impression among international health experts that increased travel by business people and tourists to endemic areas will result in more cases of inapparent malaria in donors.<sup>162</sup> In many of the published case reports,<sup>31, 47, 66, 138, 162</sup> an inaccurate donor history led to the donation of infected blood.

In the United States, prevention of transfusion-transmitted malaria depends on obtaining an accurate history from the donor of previous infection and travel to endemic areas. Donors who have a history of malaria, or who are immigrants, refugees, or former residents from endemic areas, or who have traveled to endemic areas and taken antimalarial drugs are deferred for 3 years. Individuals who have traveled to endemic areas but who have not taken antimalarial drugs can donate blood after 6 months provided that they have had no unexplained febrile illnesses. Donations of plasma that are destined for derivative production are excluded from these restrictions.

The continuing occurrence of cases of transfusion-transmitted malaria<sup>47</sup> suggests that existing standards are inadequate. An international forum on modification of existing regulations was recently published.<sup>162</sup> When the type of infecting *Plasmodium* species was reported, *P vivax* accounted for 42 per cent of cases, *P malariae* for 38 per cent of cases, and *P falciparum* for 20 per cent. Case reports analyzed by Guerrero et al<sup>66</sup> suggest that the mean interval from most recent malarial exposure to donation of infected blood was 1.4 years for *P falciparum*, 2.2 years for *P vivax*, 7 years for *P ovale*, and 11.5 years for *P malariae*. Thus, the 3-year exclusion period is effective primarily for *P falciparum* and *P vivax*. In France and Belgium, donors are screened specifically for antibodies to Plasmodia if the history suggests recent malarial exposure. Although worldwide uniform donor standards for malaria do not yet exist, international health experts are moving in that direction.

### Chagas' Disease

Chagas' disease is a parasitic disease caused by *Trypanosoma cruzi*. It most often occurs in the Americas from Mexico to Central

Argentina. In endemic areas, blood transfusions from infected asymptomatic donors may transmit the infection. Although the author could not identify any reported cases in the United States, the influx of immigrants from Central and South America has caused concern about the possibility of such infections.

A review of Chagas' disease transmitted by transfusions was recently published.<sup>131</sup> The frequency of seropositive donors varied from 0 to 22 per cent in Argentina and Brazil, with rural populations having a higher seroprevalence than urban areas. Transfusion of seropositive blood does not always result in infection. In some endemic areas, gentian violet, which kills the organism, is routinely added to blood, which is then stored for 24 hours before use. Serologic screening of donors for antibodies to *T cruzi* is performed in some areas.

Chagas' disease is certainly not an immediate threat to the blood supply of the United States. Blood centers located in areas with large immigrant populations from endemic areas may need to reassess donor screening procedures in the next 5 years.

### Babesiosis

Babesiosis is a protozoan infection caused by *Babesia microti*. The organism is transmitted through the bite of infected ticks. *B. microti* is endemic in certain areas of the northeastern United States. Nantucket Island and Cape Cod in Massachusetts, and Fire Island and eastern Long Island in New York have been identified as endemic areas. The clinical presentation of transfusion-transmitted disease is similar to the presentation of malaria. There are several case reports that describe transfusion-transmitted babesiosis infections.<sup>64, 90, 167</sup>

In endemic areas, blood collection agencies have implemented screening procedures to prevent collection of blood from donors who may transmit the infection. These are summarized by Wittner and others.<sup>167</sup> Donors with a history of babesiosis are excluded from donation. Permanent residents of Shelter Island and Nantucket are also excluded from donation. In Massachusetts, blood is not collected from endemic areas in the summer, and anyone who volunteers a history of tick bite is deferred for 3 months.

## THE RISK OF VARIOUS BLOOD PRODUCTS

Some infectious agents are strongly associated with cells, and cellular blood products, such as whole blood, red cells, platelets, and granulocytes, are more likely to transmit them. Malaria and *Babesia* species parasitize the erythrocyte. CMV may be found in peripheral blood granulocytes, lymphocytes, and monocytes. HTLV-I is also found in peripheral blood lymphocytes. Other infectious agents such as the hepatitis viruses and human immunodeficiency viruses are found in cells and plasma. Fresh frozen plasma and single-donor plasma are generally considered acellular products. However, small numbers of viable cells may persist in these products. Studies of CMV infection in open heart surgery patients who did not receive blood

but who did receive untested plasma failed to detect serologic evidence of new CMV infections. However, the author has encountered one case of graft-versus-host disease in a child with severe combined immunodeficiency transfused with maternal plasma, which had been frozen at  $-20$  degrees for several days prior to infusion (unpublished observation). Fresh frozen plasma should be considered a low-risk product, not a no-risk product, for cell-associated infections.

When infectious agents are found in plasma and cells, single-donor products are all equally likely to transmit the infection. Products manufactured from large plasma pools are more likely to transmit these infections than single-donor products. Statistically, one is more likely to encounter a seronegative donor able to transmit an infection with a pooled product. Also, there is some evidence that the screening procedure for plasma donors may not be as effective as the screening procedure for volunteer blood donors.<sup>89</sup> Plasma donors may donate every 2 to 3 weeks and thus may be more likely to transmit an infection before serum antibodies develop.

Manufacturers have worked to develop techniques that decrease the risk of infection associated with the use of pooled products.<sup>160</sup> Albumin and plasma protein solutions are heat treated at 60 degrees centigrade for 10 to 11 hours. This treatment destroys infections transmitted by transfusion. In the past, this type of treatment could not be used on clotting concentrates because it would denature the proteins. Studies in hemophilia patients reveal a high prevalence of infections with hepatitis B, HIV, and NANB hepatitis<sup>73, 74, 89, 94, 135</sup> in those who received pooled concentrates or multiple blood products.

Several techniques have been developed to inactivate viruses in plasma and clotting concentrates. Progress in this area has been summarized in a recent monograph.<sup>102</sup> The newer techniques include wet heat treatment, solvent/detergent preparation procedures, affinity chromatography, and treatment with beta-propiolactone and ultraviolet light. New products available for the treatment of hemophilia have been evaluated and recommendations made for the type of products that are most desirable.<sup>128, 163</sup> In general, pasteurized preparations and those prepared with solvent/detergent techniques appear to be the most promising at this time.

Many have been concerned that infectious agents could be transmitted in immune globulins, especially specific immune globulins. Many lots of immune globulin prepared prior to 1985 contain antibodies to HIV.<sup>127</sup> Studies indicate that immune globulin preparations, as currently manufactured in the United States, do not transmit hepatitis or HIVs. The preparation procedure eliminates viruses through partitioning and inactivation.<sup>127</sup>

### GENERAL MEASURES TO PREVENT INFECTIONS TRANSMITTED BY BLOOD

Most of the measures to prevent the infections transmitted by blood transfusion are taken at the time the blood donation is made,

Table 1. *Infections Transmitted by Transfusion*


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|                                                                                                                                                                                                                                                                                                                                                                                                                         |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Viral<br>Cytomegalovirus<br>Epstein-Barr virus<br>Hepatitis A<br>Hepatitis B<br>Hepatitis non-A, non-B<br>Human immunodeficiency virus<br>Human T-cell leukemia virus<br>Parasitic<br>Babesiosis<br>Filariasis<br>Malaria<br>Trypanosomiasis<br>Bacterial<br><i>Treponema pallidum</i><br>Other bacteria<br>( <i>Pseudomonas fluorescens</i> , <i>Yersinia enterocolitica</i> , <i>Staphylococcus</i> sp, diphtheroids) |
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and there are few specific measures that the individual physician can take to further protect his patient. However, there are a few general guidelines that every physician can take as preventive measures: (1) transfuse homologous blood only when absolutely necessary; (2) maximize the use of autologous blood: encourage preoperative autologous donation; use intraoperative salvage whenever possible; explore the possibility of postoperative wound salvage for appropriate cases; (3) report to the blood bank or transfusion service all infections thought to be related to transfusion. Donors who transmit such infections can be identified and eliminated from the donor population through investigation of transfusion-transmitted disease; and (4) evaluate the immunologic status of all patients under your care and identify patients who need blood products that are seronegative for CMV.

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## Antibiotic Therapy

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Anesthesiologists frequently practice many specialties of medicine. Although an integral part of patient care, infectious disease has not generally been considered an area of expertise of anesthesiologists. Yet, many patients come to the operating room on antibiotic therapy, and anesthesiologists frequently initiate antibiotic treatment. Therefore, it is important to understand the use of antibiotics in the perioperative period. In addition, it is essential to understand the actions, interactions, and toxicities of antibiotics relevant to the patient receiving anesthesia.

### ANTIBIOTIC PROPHYLAXIS FOR SURGERY

Antibiotic prophylaxis refers to administration of antibiotics without evidence of established infection in an attempt to decrease the postoperative septic complications. In some situations, anesthesiologists may be responsible for the prophylactic administration of antibiotics for surgery. The physical, psychologic, and economic impact of postoperative infection mandates preventive measures.<sup>55</sup> Certainly, the mainstays of prevention of infection are good operative technique and sound judgment, but well-controlled clinical studies have defined a role for antibiotic therapy.<sup>4, 56</sup>

Two groups of patients benefit from antibiotic prophylaxis. The first group includes patients who are at high risk for the development of postoperative infection. The second group includes patients who undergo procedures such as orthopedic prosthesis insertion or vascular grafting in which infection, although not frequent, may be catastrophic. The choice of antibiotic for surgical prophylaxis is based on the likely infecting organism and its susceptibility. Other considerations include possible adverse reactions and cost effectiveness.

The categorization of surgical wounds according to their suscep-

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**Table 1.** *Classification of Surgical Wounds*

| CATEGORY           | CHARACTERISTICS                                                                                                                                                                | EXAMPLES                                            |
|--------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------|
| Clean              | Elective surgery; GI, respiratory, urinary tracts not entered; primary closure; no drains; no break in aseptic technique                                                       | Inguinal herniorrhaphy, thyroidectomy, arthroplasty |
| Clean-contaminated | Bacterially colonized viscus entered with no significant spillage; no infection present                                                                                        | Cholecystectomy, gastric resection, colon resection |
| Contaminated       | Acute inflammation without pus formation; major break in aseptic technique; fresh traumatic wounds (less than 4 hours old); wounds that enter the GI tract with gross spillage | Colon resection with spillage of bowel contents     |
| Dirty              | Active infection; pus encountered; old traumatic wounds (over 4 hours old)                                                                                                     | Any wound from a dirty source                       |

tibility to infection has aided decisions regarding antibiotic prophylaxis. In 1964, the Ad Hoc Committee of the Committee on Trauma of the National Research Council promulgated a standard classification of surgical wounds as clean, clean-contaminated, contaminated, and dirty<sup>1</sup> (Table 1).

The infection rate for all types of surgical cases is approximately 5 per cent. In addition to antibiotics, factors that contribute to a decreased incidence of infection include a short preoperative stay, shaving the operative site immediately preoperatively, minimizing the duration of surgery, and a preoperative bath with an antiseptic soap.<sup>21</sup>

### Timing of Antibiotic Therapy

The administration of antibiotics is usually the responsibility of the anesthesiologist, and the timing of administration is crucial. Parenteral antibiotics should be given within 1 hour prior to surgery. If the antibiotic is given at that time, adequate serum and tissue levels of antibiotic can be obtained for the start of the operation and throughout the operative period. In addition, giving the antibiotics within 1 hour of surgery does not allow bacterial resistance to develop. Antibiotic prophylaxis is ineffective if delayed until the postoperative period.<sup>74</sup>

### Route of Administration

The usual route of administration of antibiotics for surgical patients is intravenous (IV). Whether the drug should be administered by IV bolus or by a continuous IV infusion is controversial. If the drug is administered by continuous IV infusion, there is a reduced incidence of venous irritation, phlebitis, and potential complications of rapid injection. Conversely, bolus IV administration results in higher

early concentrations of antibiotics in wound fluid. Indeed, in experimental models, high levels of antibiotics have been found in fibrin clots following bolus IV administration. This may have its clinical parallel when treating endocarditis or other infections where high tissue concentrations of antibiotics are required.<sup>2</sup> Parenteral administration of antibiotics results in adequate concentrations in pleural, peritoneal, pericardial, and synovial fluid. Therefore, direct instillation in these areas is usually not necessary.<sup>51</sup> In addition, adequate tissue levels of antibiotics can be achieved in the presence of hypotensive anesthetic techniques, despite the low perfusion pressure.<sup>60</sup>

### Duration of Treatment

The precise duration of prophylactic antibiotic therapy is controversial. It seems that within 24 hours of surgery the concentration of bacteria in wound and tissues may exceed the capacity of the unaided tissue to destroy them and heal. Therefore, a total of two to three doses of antibiotic in the perioperative period is appropriate. There appears to be no advantage to extending prophylactic antibiotic therapy beyond 24 hours in uncomplicated procedures, and it increases cost unnecessarily.<sup>32</sup> The typical 500-bed general hospital spends more than \$1 million per year to buy, prepare, and administer prophylactic antibiotics for surgery.<sup>49</sup> Aside from the health care cost, antibiotic prophylaxis should be limited to decrease the incidence of drug-related side effects and reduce the risk of infection. Indeed, the risk of infection increases if antibiotic therapy is prolonged for more than 2 days.

No single antibiotic agent or combination can be relied on for effective prophylaxis in all surgical cases. The agents employed should be chosen primarily on the basis of their safety, efficacy, and cost. Table 2 summarizes current recommendations for antibiotic prophylaxis.

**Table 2. Recommended Agents for Surgical Prophylaxis**

| PROCEDURE                                         | RECOMMENDED AGENT                                                             |
|---------------------------------------------------|-------------------------------------------------------------------------------|
| Hysterectomy                                      | Cefazolin, 1 g IV                                                             |
| Arthroplasty of joints/open reduction of fracture | Cefazolin, 1 g IV                                                             |
| Cholecystectomy                                   | Cefazolin, 1 g IV for "high risk"*<br>Neomycin and erythromycin base by mouth |
| Colon surgery                                     | Cefoxitin, 2 g IV                                                             |
| Primary appendectomy                              | Cefazolin, 1 g IV                                                             |
| Peripheral vascular surgery                       | Cefazolin, 1 g IV                                                             |
| Thoracic surgery                                  | Cefazolin, 1 g IV                                                             |

\* Over 60 years of age, previous biliary surgery, acute symptoms, or jaundice.

Adapted from Kaiser AB: Antimicrobial prophylaxis in surgery. *N. Engl J Med* 315:1129-1138, 1986.

## INFECTIVE ENDOCARDITIS

Antibiotic prophylaxis is indicated to prevent infective endocarditis in patients at risk. The risk of developing infective endocarditis is related to procedures that have a high incidence of bacteremia and to the underlying cardiac condition.

Procedures that are associated with a high incidence of bacteremia include dental procedures, upper airway manipulation, and gastrointestinal (GI) or genitourinary (GU) procedures. Prophylaxis is recommended for all dental procedures, including routine professional cleaning, that are likely to cause gingival bleeding. All surgical procedures on the respiratory tract, including tonsillectomy, with or without adenoidectomy; bronchoscopy, especially rigid bronchoscopy; and other surgical procedures, including biopsies involving the respiratory mucosa, require prophylaxis. GI or GU procedures that require prophylaxis include cystoscopy, urinary tract surgery, vaginal hysterectomy, gallbladder surgery, colon surgery, esophageal dilatation, colonoscopy, and GI endoscopy with biopsy. Prophylaxis is not necessary for percutaneous liver biopsy, barium enema, GI endoscopy without biopsy, or uncomplicated vaginal delivery. If infection is not suspected, prophylaxis is not required for dilation and curettage, cesarean section, or sterilization procedures. However, some feel prophylaxis may be prudent in patients with prosthetic heart valves.<sup>3</sup>

The risk of bacteremia resulting from endotracheal intubation has been studied by several investigators.<sup>6, 8, 9</sup> Positive blood cultures have been reported with both orotracheal and nasotracheal routes of intubation. However, the results have been inconclusive whether orotracheal or nasotracheal intubation poses a greater risk of bacteremia.<sup>8, 9</sup> Similarly, previous studies of the incidence of bacteremia associated with nasotracheal intubation are conflicting. Balch et al<sup>6</sup> found bacteremia in 33 per cent of patients after nasotracheal intubation for dental surgery. Similarly, Berry et al<sup>9</sup> found a 12 per cent incidence of bacteremia following nasal intubation in pediatric patients undergoing dental restorative procedures. Conversely, in a study by Berber et al<sup>8</sup> no patients had bacteremia after nasotracheal intubation. Recently, Dinner et al<sup>25</sup> studied the risk of bacteremia from nasotracheal intubation in order to evaluate the need for antibiotic prophylaxis in patients with structural heart lesions. Patients who are immunocompromised or have valvular heart lesions are susceptible to complications associated even with transient bacteremia, such as subacute bacterial endocarditis.) In this series, 3 of the 54 patients developed bacteremias, though none had nasal trauma during the intubation and two had topically applied vasoconstrictors. The authors conclude that nasotracheal intubation poses a risk for bacteremia that does not appear to be related to trauma to the nasal mucosa and would not be prevented by the use of topically applied vasoconstrictors.<sup>25</sup>

Cardiac conditions placing patients at risk for endocarditis can be divided into low-, intermediate-, and high-risk groups (Table 3). Low-

**Table 3. Cardiac Conditions Associated with Endocarditis**

| LOW RISK                           | INTERMEDIATE RISK                                               | HIGH RISK                                         |
|------------------------------------|-----------------------------------------------------------------|---------------------------------------------------|
| Atrial septal defect<br>Pacemakers | Mitral valve prolapse<br>Pulmonic or tricuspid<br>valve disease | Prosthetic valves<br>Patent ductus arteriosus     |
| Coronary artery bypass             | Asymmetric septal<br>hypertrophy                                | Ventricular septal defect<br>Mitral valve disease |

risk conditions do not require prophylaxis for endocarditis. The intermediate group generally warrants prophylactic therapy. In the high-risk group every precaution should be taken, and there is no doubt that patients with high-risk lesions should receive antibiotic prophylaxis. Current recommendations for antibiotic prophylaxis for endocarditis are outlined in Table 4.

### Mitral Valve Prolapse

The question of when to provide prophylaxis for patients with mitral valve prolapse (MVP) is controversial. MVP is a common dis-

**Table 4. Current Recommendations for Endocarditis Prophylaxis**

| TYPE OF PROCEDURE                            | ANTIBIOTIC THERAPY                                                                                     |
|----------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Dental and respiratory<br>Parenteral regimen | Aqueous penicillin, 2 million U IM/IV<br>Then<br>Aqueous penicillin G, 1 million U IM/IV in<br>6 hours |
| Oral regimen                                 | Penicillin V, 2 g<br>Then<br>Penicillin V, 1 g in 6 hours                                              |
| High-risk patients                           | Ampicillin, 2 g IM/IV<br>Plus<br>Gentamicin, 1.5 mg/kg IM/IV<br>Then<br>Repeat both in 8 hours         |
| Penicillin-allergic patients                 | Vancomycin, 1 g IV<br>(no repeat dose necessary)                                                       |
| GI and GU<br>Parenteral regimen              | Ampicillin, 2 g IM/IV<br>Plus<br>Gentamicin, 1.5 mg/kg IM/IV<br>Then<br>Repeat both in 8 hours         |
| Penicillin-allergic patients                 | Vancomycin, 1 g IV<br>Plus<br>Gentamicin, 1.5 mg/kg IM/IV<br>Then<br>Repeat both in 12 hours           |

*Adapted from American Heart Association Committee Report. Circulation 70:1125A, 1984.*

ease occurring in approximately 5 per cent of the population. These patients have a 5 to 8 times greater risk of developing infective endocarditis than patients without cardiac disease.<sup>14</sup> Still, prophylaxis for all patients with MVP is not warranted because it is not cost effective and anaphylactic reactions to antibiotics are always a possibility. All patients having MVP associated with a murmur should be offered prophylaxis for infective endocarditis. Patients with silent MVP are at no apparent increased risk; therefore, antibiotic therapy is not indicated. Prophylaxis for patients with an isolated click without a murmur or patients who have echocardiographic evidence of mitral regurgitation without a murmur remains controversial. In the absence of an allergic history, most clinicians usually provide prophylaxis for these patients.<sup>43</sup>

### Rheumatic Fever

Occasionally, patients who are receiving antibiotic treatment to prevent rheumatic fever will present for surgery. It should be noted that continuous low-dose penicillin used to prevent rheumatic fever is inadequate prophylaxis for infective endocarditis.<sup>26</sup> Also, patients who receive prophylaxis for rheumatic fever may develop resistant strains of bacteria. Therefore, when providing prophylaxis for endocarditis, the parenteral route should be used and vancomycin should be considered as an alternate regimen.

## ANTIMICROBIALS

### Penicillins

Penicillins can be divided on the basis of antibacterial activity (Table 5). They generally inhibit cell wall biosynthesis through penicillin-binding proteins and are bacteriostatic. Most anaerobic gram-positive bacteria are susceptible to all the penicillins. Gram-negative

**Table 5.** *Classification of Penicillins*

| CLASSIFICATION                                                  | EXAMPLES                                                                        |
|-----------------------------------------------------------------|---------------------------------------------------------------------------------|
| I. Natural penicillins                                          | Penicillin G, penicillin V, phenethicillin                                      |
| II. Penicillinase-resistant penicillins, isoxazolyl penicillins | Methicillin, nafcillin<br>Oxacillin, cloxacillin, dicloxacillin, flucloxacillin |
| III. Aminopenicillins                                           | Ampicillin, amoxacillin, bicampicillin, hetacillin                              |
| IV. Antipseudomonas penicillins                                 | Azlocillin, carbenicillin, ticarcillin                                          |
| V. Extended-spectrum penicillins                                | Mezlocillin, piperacillin                                                       |
| VI. Amidino penicillins                                         | Amdinocillin, pivaminopenicillin                                                |
| VII. Stable against gram-negative $\beta$ -lactamases           | Temocillin                                                                      |

anaerobic bacteria are susceptible to most penicillins with the exception of *Bacteroides fragilis*, which is inhibited by high levels of penicillin G or the antipseudomonas and extended spectrum penicillins. *Fusobacterium varium* often is resistant to all penicillins. All penicillins are excreted into urine via renal tubular cells. In addition, most penicillins are actively secreted into the bile resulting in significantly higher biliary than serum concentrations.

The major adverse effect of the penicillins is hypersensitivity. Reactions range in severity from rash to immediate anaphylaxis. Indeed, allergic reaction to penicillin is the most common cause of anaphylaxis, a rare occurrence but potentially fatal. Patients with atopic dermatitis or allergic rhinitis appear to be at no increased risk for developing anaphylaxis. Other adverse effects of penicillins include diarrhea, neutropenia, autoimmune hemolytic anemia, and impaired platelet aggregation, although bleeding is a rare occurrence. Neurologic manifestations of toxicity include myoclonic seizures. Renal damage ranging from allergic angitis to interstitial nephritis has been described. Electrolyte abnormalities are an important consideration when using penicillins. Hypokalemia can result from use of carbenicillin or ticarcillin because they serve as nonreabsorbable anions. In addition, a large sodium load is given to the patient with carbenicillin and ticarcillin because these agents are disodium salts and contain 5 mEq per g of sodium. An alternative regimen would include a drug such as azlocillin, which is a monosodium salt with half the salt load. Hyperkalemia or hyponatremia can result from large-dose penicillin G administration because each million units has approximately 1.7 mEq of potassium or sodium, depending on the preparation.

### Cephalosporins

Cephalosporins are the most commonly used agents for surgical prophylaxis. Indeed, they are the most frequently prescribed antimicrobials. These agents are divided into a well-accepted generation scheme (Table 6). The first-generation cephalosporins provide good gram-positive coverage and may also be used to treat infections caused by some gram-negative and nonbacteroides anaerobic organisms. Second-generation cephalosporins generally display increased activity against gram-negative organisms but agents grouped in this class present a wide range of antibacterial and pharmacologic properties. Third-generation cephalosporins offer less gram-positive coverage than first-generation agents but have increased activity against aerobic

Table 6. Classification of Cephalosporins

| CLASSIFICATION    | EXAMPLES                                           |
|-------------------|----------------------------------------------------|
| First generation  | Cefazolin, cephalothin, cephapirin, cephadrine     |
| Second generation | Cefamandole, cefoxitin, cefuroxime, cefaclor       |
| Third generation  | Cefotaxime, ceftazidime, cefoperazone, ceftriaxone |

gram-negative rods and Enterobacteriaceae including the penicillinase-producing strains. Certain third-generation agents are active against *Pseudomonas aeruginosa*.

Because the chemical structures of cephalosporins and penicillins are similar, cross reactivity between the two drugs is not uncommon. Indeed, immunologic studies indicate that as many as 20 per cent of patients show cross reactivity. Clinically, however, only 5 to 10 per cent show cross allergy with penicillin. Therefore, if the penicillin allergy is not an anaphylactic type, cephalosporins may be given.

Other side effects of cephalosporin administration include nephrotoxicity and hematologic abnormalities. Interstitial nephritis may result from cephalosporin therapy, especially in patients over the age of 60 years. There is evidence to suggest that the combination of a cephalosporin and an aminoglycoside potentiates nephrotoxicity. A positive Coomb's test occurs in approximately 3 per cent of patients receiving cephalosporins, although it is rarely accompanied by hemolytic anemia. A serious bleeding diathesis with hypoprothrombinemia and qualitative or quantitative platelet abnormalities may occur with cephalosporin therapy, especially treatment with moxalactam.

### Aminoglycosides

Aminoglycosides bind irreversibly to proteins in the ribosomes, causing interruption of the flow of genetic information,<sup>38</sup> so these agents are bactericidal. Most aminoglycosides inhibit members of the Enterobacteriaceae. When initiating therapy, a loading dose should be administered to achieve a therapeutic serum level rapidly. The clearance of aminoglycosides is linearly related to creatinine clearance. While quantitative differences among individual agents may exist, all aminoglycosides share three toxicities: (1) neuromuscular paralysis; (2) ototoxicity; and (3) nephrotoxicity.

**Neuromuscular Paralysis.** Aminoglycoside-induced neuromuscular paralysis is a rare but potentially lethal complication. It should be suspected if there is delayed recovery from a nondepolarizing neuromuscular blocking agent, the depth of neuromuscular blockade increases following antibiotic administration, or the neuromuscular block is difficult to reverse. The mechanism whereby aminoglycosides potentiate neuromuscular blockade is both inhibition of presynaptic release of acetylcholine and a blockade of postsynaptic receptor sites for acetylcholine. This block is enhanced by the presence of curare-like drugs, succinylcholine, magnesium, and in patients with myasthenia gravis. The block is reasonably well reversed with calcium administration and partially reversed with neostigmine.<sup>72</sup>

**Ototoxicity.** All aminoglycosides are capable of producing ototoxicity. Although individual agents can preferentially produce auditory or vestibular toxicity, all aminoglycosides are capable of producing both. Ototoxicity is potentiated by other agents, including ethacrynic acid, furosemide, and possibly other diuretics. The toxicity seems best correlated with the duration of aminoglycoside therapy, preexisting renal disease, and the age of the patient. Ototoxicity has

been reported to occur in approximately 5 per cent of patients receiving aminoglycoside therapy.<sup>29</sup>

**Nephrotoxicity.** All aminoglycosides may be nephrotoxic. Clinical nephrotoxicity as defined by a fall in glomerular filtration rate occurs in 5 to 25 per cent of patients receiving aminoglycosides.<sup>71</sup> It is important to monitor serum levels when patients are maintained on aminoglycoside therapy. Risk factors for nephrotoxicity include advanced age, prior aminoglycoside administration, preexisting renal dysfunction, concomitant administration of other nephrotoxic agents, hypotension, and prolonged administration of the drug.

### **Vancomycin**

Vancomycin is a glycopeptide with activity directed against gram-positive organisms. It is bactericidal and inhibits cell wall synthesis. The half-life of vancomycin is 6 hours with elimination of the drug via glomerular filtration. The most common side effects of vancomycin administration are fever, chills, or phlebitis at the site of infusion. Ototoxicity manifest as eighth nerve damage is possible. A more serious complication is the "red-neck syndrome" following rapid infusion of the drug. This is a histamine-induced reaction characterized by flushing and a maculopapular rash of the face, neck, and trunk. It is usually a self-limited reaction and abates with cessation of the drug. Occasionally antihistamines and fluid resuscitation are necessary.<sup>53</sup> It appears to be related to the rate of administration so that the drug must be infused slowly over 1 hour.

### **Clindamycin**

The major therapeutic use for this lincosamine antibiotic is for anaerobic infections or in combination with an aminoglycoside or aztreonam. The most common and serious side effect of clindamycin is diarrhea with pseudomembranous colitis, which occurs in as many as 10 per cent of clindamycin-treated patients.<sup>77</sup> Drug rashes occur in approximately 5 per cent of patients. Itching, angioneurotic edema, urticaria, Stevens-Johnson syndrome, drug fever, and granulocytopenia have been reported. Abnormalities in liver function tests, particularly transaminase elevations, appear frequently. However, they are usually erratic, mild, and unassociated with other evidence of hepatotoxicity. As with aminoglycosides, clindamycin can cause potentiation of neuromuscular blockade, although much less frequently. Clindamycin is incompatible in solution with many commonly used drugs such as ampicillin, barbiturates, aminophylline, calcium gluconate, magnesium sulfate, and diphenylhydantoin.

### **Metronidazole**

Metronidazole is a nitroimidazole with potent bactericidal properties. It is most useful in the treatment of serious anaerobic infections, especially intra-abdominal infections. Metronidazole has no activity against gram-positive or gram-negative aerobic organisms. There is

little protein binding, and it has a half-life of 8 hours. Metronidazole is metabolized in the liver and eliminated in the urine and the feces.

Side effects of metronidazole therapy include a disulfiram reaction, potentiation of warfarin, and pseudomembranous colitis. However, colitis is a rare complication, and metronidazole is used as an alternative to vancomycin to treat pseudomembranous colitis. Neurologic manifestations such as seizures, encephalopathy, and neuropathy occur rarely.

### Imipenem

Imipenem is a prototype of the thienamycin class of compounds, a carbapenem antibiotic. It offers broad-spectrum coverage with potent activity against most clinically important species of bacteria, including isolates resistant to other antibiotics. It generally will distribute to most tissues and body fluids following intravenous administration though cerebrospinal fluid levels are modest. Most of the drug is eliminated in the urine where it is metabolized by an enzyme located on the brush border of the renal tubular cells. Cilastatin is given simultaneously to inhibit this inactivation. The drug is generally well tolerated though several adverse effects have been described. Approximately 3 per cent of patients manifest allergic reactions as drug fever, pruritis, or urticaria. Nausea and vomiting, diarrhea, and abnormalities of liver function have been described. More serious adverse effects such as seizures and superinfection have also been reported.<sup>7</sup>

### Quinolones

The quinolones represent a group of antibacterial agents with the most innovative development. The first generation of quinolones never gained widespread acceptance because of limited effectiveness against many organisms. However, development of the newer generation quinolones such as ciprofloxacin has created new interest in the class of drugs. Newer fluorinated quinolones such as ofloxacin, enoxacin, norfloxacin, and fleroxacin are currently undergoing investigation. These newer agents have a much broader spectrum of activity than the early quinolones including efficacy against gram-negative bacteria and *Staphylococcus aureus*. They have only limited activity against *Bacteroides fragilis* and aerobic staphylococci. The distribution and tissue penetration of quinolones are excellent.

The most common indications for the use of fluorinated quinolones include urinary tract infections, prophylaxis for urosurgery, gonorrhea, and bacterial enteritis. Quinolones have also been used successfully to treat chronic osteomyelitis caused by gram-negative species,<sup>35, 37, 70</sup> soft-tissue infections caused by a wide range of gram-positive cocci, pseudomonas, and enterobacteriaceae,<sup>28, 31, 34, 81</sup> and have been useful both prophylactically and therapeutically in neutropenic patients.

The side effects most often seen with quinolones usually relate to the GI tract, the central nervous system, and the urinary tract. In-

deed, the most frequent complaints during the use of quinolones are nausea, upper GI discomfort, and dizziness. These reactions are usually mild and rarely necessitate changing to another antibacterial agent. Another phenomenon noted with quinolone therapy is the formation of quinolone crystals in the urine. The consequence of quinolone crystals is uncertain at present, though deleterious effects of these crystals have not been described to date.

Because quinolones are orally administered broad-spectrum antimicrobial agents, they have considerable potential for significant cost reduction. These agents reduce the supplies and equipment necessary for parenteral administration, and health personnel work time is less. Oral dosage forms have less potential for iatrogenic consequences than IV forms. Because quinolones are broad-spectrum agents, multiple drug regimens are not necessary. Finally, development of resistance appears to be less of a problem with quinolones, and they are ecologically more favorable since the normal microflora is little affected.

### **Aztreonam**

This is the first of a new class of monocyclic  $\beta$ -lactams. The activity of aztreonam is specifically directed against aerobic gram-negative bacteria. The pharmacologic properties of this agent are not exceptionally different from other parenterally administered  $\beta$ -lactam antibiotics that are not absorbed orally.<sup>75, 76</sup> Dosage must be adjusted in patients with renal failure, cirrhosis, and during dialysis. In patients with renal failure the usual initial dose is given and subsequent doses are reduced to a quarter of the normal dose.<sup>50</sup> An additional one-eighth dose can be given after dialysis. In severe alcoholic cirrhosis the dosage should be reduced by 20 to 25 per cent, but reduced dosages seem not to be required in other forms of liver disease.<sup>46</sup>

Aztreonam is an effective agent in severe gram-negative bacterial infections. The types of infections for which aztreonam should be considered as a single agent include urinary tract or biliary tract infections, gonorrhea, and gram-negative osteomyelitis. It should be considered in combination with other agents for abdominal sepsis, respiratory tract infections, septicemia in leukemics and neonatal meningitis. In studies where aztreonam was used in combination with other agents, it did not impair the activity of penicillin, erythromycin, or vancomycin nor did these agents interfere with other activity of aztreonam.

Hypersensitivity reactions are an important limitation of the use of  $\beta$ -lactam antibiotics. However, several studies suggest there is very little cross reactivity between aztreonam and other  $\beta$ -lactam antibiotics. The most common reported side effects are local reactions, skin rash, nausea, and diarrhea. The overall incidence of side effects and abnormal laboratory results necessitating discontinuation of aztreonam is approximately 2.1 per cent.<sup>54</sup>

Although extensive work has been done on structure-activity relationships of monocyclic  $\beta$ -lactams,<sup>13</sup> aztreonam is the only agent

currently available for patient use. Newer compounds are being developed and further derivations will surely emerge.<sup>48, 52</sup>

### **$\beta$ -Lactamase Inhibitors**

$\beta$ -lactamases account for the major form of resistance to penicillins and cephalosporins. Because it has been difficult to develop antibiotics with stability to a wide range of  $\beta$ -lactamases, combinations of an antibiotic with a  $\beta$ -lactamase inhibitor have recently gained popularity. Clavulanate is a  $\beta$ -lactamase inhibitor with little antibacterial activity of its own. It inhibits  $\beta$ -lactamases with destruction of the enzyme. The combination of amoxacillin and clavulanate has been used successfully to treat skin infections, otitis, and upper respiratory infections. The combination does not significantly alter the pharmacologic properties of either drug. The combination of ticarcillin and clavulanate has been shown to be effective in the treatment of intra-abdominal infections, osteomyelitis and urinary tract infections, because of the increased activity of ticarcillin when used in conjunction with clavulanate. The combination has also been used as therapy for the febrile neutropenic patient.

Sulbactam is a 6-desamino penicillin sulfone that also inhibits  $\beta$ -lactamases. Sulbactam has pharmacokinetics similar to ampicillin. Combined with ampicillin, this agent has been used successfully to treat urinary, intra-abdominal, and respiratory infections caused by  $\beta$ -lactamase-producing organisms.

## **ANTIVIRAL AGENTS**

Several antiviral agents with proven efficacy against infections due to influenza A, herpes simplex virus (HSV), and varicella zoster virus (VZV) are currently available. However, most antiviral agents have a restricted spectrum of activity because of selective inhibition of specific events in viral replication. In addition, most agents are ineffective in the elimination of latent or nonreplicating viruses since antivirals generally inhibit ongoing replication at the host cell level. Further, the development of viral resistance to antiviral agents may limit their effectiveness.<sup>18, 19, 42, 69</sup> Combinations of antiviral agents have been used successfully to increase efficacy and decrease toxicity.<sup>27, 40, 45, 63, 66, 67, 73, 80</sup>

Pharmacokinetic studies of absorption, stability, tissue distribution, and metabolic fate of antiviral agents aid in the selection of the choice and dose of antiviral agent. Unfortunately, no standardized or generally accepted correlations exist between in vitro inhibitory concentrations, achievable blood or body fluid concentrations of antiviral agents, and clinical response.<sup>39</sup> Animal models are helpful although many differ with respect to pathogenesis, drug sensitivity, pharmacology, and toxicity compared to human infection.<sup>36</sup> The antiviral agents most commonly in use today include acyclovir, amantadine, vidarabine, idoxuridine, and trifluridine (Table 7).

**Table 7. Commonly Used Antiviral Agents**

| INFECTION                                      | AGENT                                  |
|------------------------------------------------|----------------------------------------|
| HSV encephalitis                               | Vidarabine                             |
| Neonatal HSV                                   | Vidarabine                             |
| Herpes zoster<br>(immunocompromised hosts)     | Vidarabine (acyclovir)                 |
| Herpes zoster<br>(normal hosts)                | Acyclovir                              |
| Varicella<br>(immunocompromised hosts)         | Vidarabine                             |
| Genital HSV                                    | Acyclovir                              |
| HSV keratoconjunctivitis                       | Idoxuridine (vidarabine, trifluridine) |
| Mucocutaneous HSV<br>(immunocompromised hosts) | Acyclovir                              |
| Influenza A virus                              | Amantadine (rimantadine)               |

*Adapted from* Hyden FG, Douglas RG: Antiviral Agents. *In* Mandell GL (ed): Principles and Practice of Infectious Diseases. New York, Wiley, 1985, p 271.

### Acyclovir

Acyclovir is an acyclic analogue of the natural nucleoside, 2'-deoxyguanosine. Its antiviral activity is primarily directed at HSV types 1 and 2, VZV, and Epstein-Barr virus.<sup>17, 20, 62</sup> The mechanism of action involves inhibition of viral DNA synthesis. Alterations in either the viral thymidine kinase or DNA polymerase cause acyclovir resistance *in vitro*.<sup>15, 64</sup> Approximately 70 per cent of acyclovir is excreted unchanged in the urine,<sup>24</sup> with less than 15 per cent excreted as minor metabolites.<sup>11, 22, 23</sup> IV administration is generally well tolerated.<sup>5, 78</sup> Irritation at the site of injection, rash, nausea, central nervous system changes, and renal dysfunction have all been described with acyclovir administration.

### Amantadine

Amantadine is a symmetric amine with specific activity against influenza A viruses. It probably exerts its antiviral activity by inhibition of viral replication in an early stage. Amantadine is available only in oral formulations. It is well absorbed, not metabolized, and has a serum half-life of 14 hours. Following oral administration 95 per cent of the dose appears in the urine unchanged. The major toxicity of amantadine relates to the central nervous system effects, including anxiety, insomnia, and difficulty in concentration.<sup>41</sup> The effects are probably related to its dopamine potentiating properties.<sup>57, 65</sup> Other potential toxicities include nausea, edema, livido reticularis, congestive heart failure, and urinary retention.

### Vidarabine

Vidarabine is an analogue of adenine deoxyriboside with *in vitro* activity against HSV types 1 and 2, VZV, Epstein-Barr virus, and some

RNA tumor viruses.<sup>10, 12, 16, 30, 33, 68</sup> The drug is phosphorylated by host cell enzymes to form a triphosphate derivative that inhibits HSV DNA polymerase and may also result in premature termination of elongating DNA chains. The primary route of elimination is renal, with urinary excretion accounting for 50 per cent of the dose. Most of the drug is excreted as hypoxanthine arabinoside. GI toxicity not uncommonly manifests as anorexia, nausea, vomiting, and diarrhea.<sup>61, 79</sup> At higher doses, vidarabine has been associated with hematopoietic abnormalities and neurotoxicities such as anemia, leukopenia, thrombocytopenia, tumors, seizures, and unusual pain syndromes in the extremities.<sup>44, 47, 59</sup>

### Interferons

Interferons are proteins or glycoproteins produced by cells in response to an inducer, including viruses. There are currently numerous trials testing the efficacy of various interferons against not only viruses but also malignancies. This work along with studies of newer antiviral agents will determine the role of these agents in the future.

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## Principles of Sterilization and Disinfection

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The purpose of this article is to describe the basic principles of sterilization and disinfection as well as the factors that govern their efficacy. Strategies that are used in health care facilities are described and there is a focus on application of strategies for sterilization and disinfection applied to anesthesiology equipment. Precise protocols for specific types of anesthesia equipment as well as the potential for these systems of transmitting infections from patient to patient or patient to staff member will be discussed in the article on cleaning and processing of anesthesia equipment.

The effective use of antiseptics, disinfectants, and sterilization procedures in health care settings is important in the prevention of hospital-acquired infections. Historically, the use of physical agents such as moist heat in the form of steam autoclaves or dry heat sterilizers has played the predominant role for sterilizing devices, equipment, and supplies in hospitals.<sup>5, 6</sup> Gaseous sterilization by ethylene oxide sterilizers also has become popular for sterilizing items that are heat sensitive. There are a number of newly developed sterilization procedures meant to replace ethylene oxide sterilization that include the use of hydrogen peroxide vapors and plasmas as well as formulations of hydrogen peroxide and paracetic acid. Chemical germicides used for cold sterilants have also been on the market for many years in the United States but currently are used to disinfect rather than sterilize medical devices.

The choice of what sterilization procedure or disinfection method or which specific chemical germicide should be used for sterilization, disinfection, or antisepsis or for environmental sanitation depends on a great many factors. No single chemical germicide or agent or procedure is adequate for all purposes. Factors that should be considered in the selection of a specific sterilization or disinfection procedure include (1) the degree of microbiologic inactivation required for the particular device, (2) the nature and physical composition of

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the device being treated, and (3) the cost and ease of using a particular procedure. In this article, each of these factors will be discussed in the context of anesthesiology equipment. In addition, there will be a brief discussion on the regulation of chemical germicides by United States governmental agencies. Various levels of antimicrobial effectiveness will be described as well as criteria that can be used in the selection of chemical germicides.

## REGULATION OF CHEMICAL GERMICIDES

The primary agency in the United States federal government that is involved with disinfection and sterilization procedures and devices is the Environmental Protection Agency (EPA). This agency approves sterilizers such as steam autoclaves and ethylene oxide sterilizers. In addition, chemical germicides that are formulated as sterilants and disinfectants (germicides used on devices or environmental surfaces) are regulated and registered by EPA. The EPA requires manufacturers of chemical germicides formulated as general disinfectants, hospital disinfectants, and disinfectants applied to other environments to test these formulations using specific and standardized protocols for microbicidal efficacy, stability, and toxicity to humans.

Chemical germicides that are formulated as antiseptics, preservatives, or drugs to be used on or in the human body or as preparations to be used to inhibit or kill micro-organisms on the skin are regulated by the Food and Drug Administration (FDA). The FDA has an advisory panel that reviews nonprescription antimicrobial drug products. Manufacturers of such formulations voluntarily submit data to the panel, which in turn categorizes the products for their intended use, that is, antimicrobial soaps, health care personnel handwashes, patient preoperative skin preparations, skin antiseptics, skin wound cleansers, skin wound protectants, and surgical hand scrubs. General chemical germicides for each use are further divided into three categories: category I, safe and efficacious; category II, not safe or efficacious; and category III, insufficient data to categorize.

Chemical germicides formulated as antiseptics are categorized basically by use and efficacy and are not regulated or registered in the same fashion that EPA regulates and registers a disinfectant. Currently, many of the antimicrobial antiseptic formulations on the market are in category III, which means that health care workers must make decisions based on information derived from the manufacturer or in published studies in the literature.

The Centers for Disease Control (CDC) does not approve, regulate, or test chemical germicides formulated as disinfectants or antiseptics. Rather, the CDC recommends broad strategies for the use of sterilants, disinfectants, and antiseptics to prevent transmission of infections in the health care environment.<sup>7</sup>

## DEFINITIONS

The definitions of sterilization, disinfection, antisepsis, and other related terms such as decontamination and sanitization are generally accepted in the scientific community but some of these terms are misused. It is important not only to understand the definition and inferred capabilities of each procedure, but also to understand how to achieve and in some cases monitor each state.

### Sterilization

The term “sterilization” is one that students and professionals have memorized and recited seemingly forever. It can be the simplest and the most complex concept depending on how it is viewed and how it is applied. The definition of sterilization can change depending on the vantage point from which it is viewed. I choose to view this term somewhat like a hologram and will define it in the context of the *state* of sterilization, the *procedure* of sterilization, and the *application* of sterilization.

An item, device, or solution is considered to be sterile when it is completely free of all living micro-organisms. This *state* of sterility is the objective of the sterilization procedure and when viewed in this context, the definition, for all practical purposes, is the categorical and absolute definition—an item is either sterile or it is not.

A sterilization *procedure* is one that kills all micro-organisms including high numbers of bacterial endospores. Sterilization can be accomplished by heat, ethylene oxide gas, radiation (in industry), and by a number of liquid chemical germicides, notably those approved by the EPA as cold sterilants. Sterilization procedures from an operational standpoint cannot be categorically defined. Rather the procedure is defined as a process, after which the probability of a micro-organism surviving on an item subjected to the sterilization procedure is less than one chance in a million ( $10^{-6}$ ). It is this approach that is used by the medical device industry to sterilize large quantities of medical devices. Some criteria used in the production and labeling of a sterile device are listed in Table 1.

The application of sterilization principles in industry is much more sophisticated and controlled than sterilization procedures used

Table 1. *Criteria Used in Producing Sterile Devices*

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|                                                                                         |
|-----------------------------------------------------------------------------------------|
| Good manufacturing practices                                                            |
| Validated sterilization process                                                         |
| Use of biological indicators                                                            |
| Sterility testing of a subsample of the batch subjected<br>to the sterilization process |
| Process controls                                                                        |
| Quality control of materials                                                            |
| Poststerilization testing of devices for function                                       |

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in health care environments. However, steam autoclaves, ethylene oxide sterilizers, and dry heat sterilization ovens used in health care facilities have operational protocols that are verified by the manufacturer to accomplish sterilization and all the variables that control for the inactivation of micro-organisms are either automated or built into simple controls in the devices.

The *application* of the sterilization process takes into account additional considerations. This approach involves the strategy associated with a particular medical device or solution and the context of its exposure to humans. Almost 30 years ago, Spalding proposed that the nature of device and equipment sterilization and disinfection could be understood more readily if medical devices, equipment, and surgical materials are divided into three categories based on the risk of infection involved in their use. Briefly, devices that are exposed to sterile areas of the body, such as blood, require sterilization; devices that touch mucous membranes may be either sterilized or disinfected; and devices or items that touch skin or environmental surfaces can be sanitized with a low-level disinfectant or simply cleaned with soap and water.<sup>5, 6</sup>

In the context of these categorizations, Spalding also classified chemical germicides by activity level. The activity levels are listed in Table 2 and are as follows.

**High-Level Disinfection.** A procedure that kills vegetative micro-organisms but not necessarily high numbers of bacterial spores. These chemical germicides, by Spalding's definition, are those that are capable of accomplishing sterilization, that is, kill all micro-organisms including a high number of bacterial spores, when the contact time is relatively long (6 to 10 hours). As high-level disinfectants they are used for relatively short periods of time (10 to 30 minutes). These chemical germicides are those that are registered with the EPA as sterilant/disinfectants.

**Intermediate-Level Disinfection.** A procedure that kills vegetative micro-organisms including *Mycobacterium tuberculosis*, all fungi, and most viruses. These chemical germicides often correspond to EPA approved "hospital disinfectants" that are also "tuberculocidal."

Table 2. Levels of Germicidal Action

| LEVEL        | BACTERIA               |                      |        | FUNGI | VIRUSES                          |                          |
|--------------|------------------------|----------------------|--------|-------|----------------------------------|--------------------------|
|              | Vegetative<br>Bacteria | Tubercle<br>Bacillus | Spores |       | Lipid<br>and<br>Medium-<br>sized | Nonlipid<br>and<br>small |
|              |                        |                      |        |       |                                  |                          |
| High         | +                      | +                    | +      | +     | +                                | +                        |
| Intermediate | +                      | +                    | ±      | +     | +                                | ±                        |
| Low          | +                      | -                    | -      | ±     | +                                | -                        |

**Table 3.** Centers for Disease Control and Environmental Protection Agency Classification Schemes for Sterilants, Disinfectants, and Sanitizers

| EPA PRODUCT CLASSIFICATION                                           | TYPE OF DEVICE OR SURFACE                                                      | CDC PROCESS CLASSIFICATIONS                                       |
|----------------------------------------------------------------------|--------------------------------------------------------------------------------|-------------------------------------------------------------------|
| Sterilant/disinfectant                                               | Critical (IV catheter, spinal needles)                                         | Sterilization (sporicidal chemical, prolonged contact time)       |
|                                                                      | Semicritical (reusable anesthesia circuits, endotracheal tubes, laryngoscopes) | High-level disinfection (sporicidal chemical, short contact time) |
| Hospital disinfectant (with label claim for tuberculocidal activity) | Noncritical (blood contaminated control knobs of anesthesia machines)          | Intermediate-level disinfection                                   |
| Hospital disinfectant Sanitizer                                      | Noncritical (exterior of machines, housekeeping, floors)                       | Low-level disinfection or soap and water                          |

**Low-Level Disinfection.** A procedure that kills most vegetative bacteria except *M. tuberculosis*, some fungi, and some viruses. These chemical germicides are often ones that are approved by EPA as "hospital disinfectants" or "sanitizers."

The relationship between EPA's system of classification and CDC's recommendation for strategies of sterilization and disinfection is also shown in Table 3.

Spalding's system for classifying devices and strategies for disinfection and sterilization is quite conservative. There is a direct relationship between the degree of conservatism as expressed by the probability of a micro-organism surviving a particular procedure and microbicidal activity. For example, a sterilization procedure accomplished by either steam autoclaving, dry heat sterilization, or ethylene oxide gas sterilization by definition has a probability of one in a million of a surviving micro-organism remaining if the procedure had initially been challenged with  $10^6$  highly resistant bacterial spores. The risk of infection resulting from the use of an item that was subjected to this type of procedure, assuming that the procedure had been carried out properly, would appear to be zero. Correspondingly, the probability of contamination and the estimated theoretical probability of infection associated with chemical sterilization, high-level disinfection, or low-level disinfection would increase as the germicidal activity of the procedure in question decreased.

A process of chemical sterilization at best would have three orders of magnitude less reliability than conventional heat sterilization. From a practical standpoint, this means that there is a lower level of confidence with such procedures and if and when mistakes are made, there is a higher chance of failure than with a heat sterilization procedure. It also would appear that when errors are made, they have

much more of a consequence when a procedure of high-level disinfection or intermediate-level disinfection rather than a sterilization procedure is used. The procedures that contain less built-in insurance are procedurally driven and are ones that are usually associated with very precise protocols, policies, and monitoring.

### **Decontamination**

Another term that is quite often used in health care facilities is "decontamination." A process of decontamination is one that renders a device, items, or materials safe to handle; safe in the context of reasonably free of the probability of transmission of infection. The actual process sometimes is a sterilization procedure such as steam autoclaving. Often this may be the most cost-effective way of decontaminating a device or an item. On the other hand, it may simply be soap and water cleaning of an instrument, a device, or an area. When chemical germicides are used for decontamination, they can range in activity from sterilant/disinfectants, which might be used to decontaminate spills of highly infectious agents in research or clinical laboratories, to low-level disinfectants or sanitizers when environmental surfaces or infectious wastes are involved.

### **Antiseptic**

The term "antiseptic" is used to describe a substance that has antimicrobial activity and is formulated to be used on or in living tissue to inhibit or destroy micro-organisms. Quite often the distinction between an antiseptic and a disinfectant is not made. However, the differences between a disinfectant and an antiseptic are very great and applications are significantly different. A disinfectant is a chemical germicide that is formulated to be used solely on medical devices, instruments, and environmental surfaces. An antiseptic is a chemical germicide that is formulated to be used solely on or in living tissues. Some chemical agents such as iodophors can be used as active ingredients in chemical germicides that are formulated both as disinfectants and as antiseptics. However, the precise formulations are significantly different, are used differently, and the germicidal efficacy of each formulation differs substantially. Consequently, disinfectants should never be used as antiseptics and vice versa.

## **FACTORS THAT INFLUENCE GERMICIDAL ACTIVITY**

Micro-organisms show a wide variance in their resistance to sterilants and disinfectants. The most resistant micro-organisms are bacterial endospores and few, if any, other micro-organisms approach the broad resistance of these organisms. A number of factors, some of which are associated with micro-organisms themselves and others with the surrounding physical and chemical environment, can significantly influence the antimicrobial efficacy of chemical germicides.

Some factors are more important than others but all of them should be considered when planning sterilization and disinfection strategies for medical and surgical devices and materials. Briefly, these factors are listed.

—The type of micro-organism: bacterial spores are more resistant than mycobacteria, fungi, vegetative bacteria, and viruses; some types of viruses are more resistant to germicides than others. As a general guide, one should define the state or degree of inactivation needed (that is, sterilization) and then choose the procedure.

—The number of micro-organisms: all other factors being equal, the greater the number of micro-organisms present on a device, the longer it takes to inactivate this microbial population. It is for this reason that devices, especially those that are disinfected, should be cleaned prior to being sterilized or disinfected.

—The intrinsic resistance of micro-organisms: bacterial spores have already been mentioned but very few of them are actually responsible for hospital acquired infections. However, there are organisms such as *M. tuberculosis*, nontuberculosis mycobacteria, as well as naturally occurring gram-negative water bacteria such as *Pseudomonas aeruginosa* and *P. cepacia* that can under some circumstances be relatively resistant to chemical disinfectants. After bacterial spores, *M. tuberculosis* is considered the most resistant class of micro-organisms. It is for this reason that chemical germicides that have been approved as “tuberculocides” are sometimes recommended for purposes of decontamination or disinfection when a higher activity germicide is sought. It is usually not a fear of transmission of *M. tuberculosis* but rather a definition or specification that can be used to describe a germicide with a relatively high level of germicidal activity.

—There are a number of other factors including temperature, organic load, pH, germicide concentration, and inorganic load that can influence the rate of inactivation of micro-organisms by chemical germicides. For these reasons, items and devices are precleaned prior to disinfection and sterilization. Additionally, precise protocols and directions on product labels are very important, especially with liquid chemical germicides, and must be closely adhered to.

—The device that is being sterilized or disinfected must be compatible with the procedure so that device material is not degraded or its functions impaired. The manufacturers of the device and the chemical germicide are the best sources of information regarding compatibility.

### **SPECIAL APPLICATIONS OF STERILIZATION AND DISINFECTION STRATEGIES TO ANESTHESIOLOGY EQUIPMENT**

For many years, anesthesiology machines and associated equipment had been lumped with inhalation therapy equipment. In this context, there was a great deal of concern not only about the types of micro-organisms that could be transmitted from patient to patient mediated by anesthesiology equipment, but also types of micro-organisms that could become colonized in inhalation therapy equipment, grow to large numbers, and act as pathogens to patients. This general

extrapolation of principles based on inhalation therapy equipment to anesthesia equipment, in some respects, is not justified. The literature suggests that the anesthesia machine and associated circle system do not act as a reservoir of micro-organisms such as *P. aeruginosa* and *P. cepacia*, which have the capability of growing in water systems. These bacteria have been associated with improperly disinfected inhalation therapy equipment, which may act as source of microbial contamination. In short, the anesthesia machine per se does not appear to be a significant reservoir of bacteria associated with infection.<sup>3, 4</sup>

Consequently, routine cleaning and sterilization procedures that have been described by the AORN<sup>1</sup> and the CDC<sup>7</sup> are sufficient to prevent the transmission of infection from patient to patient and from machine to patient in this setting. Further, there does not appear to be any reason to routinely clean or disinfect the internal parts of the anesthesia machine beyond the normal maintenance requirement specified by the manufacturer. Certain parts such as soda lime canisters should be replaced when specified by the manufacturer or when their function is exhausted but changing frequencies are not influenced by consideration of transmission of infectious agents. In general, the standard protocols, procedures, and strategies that have been recommended for disinfecting or sterilizing items associated with anesthesiology are based on fairly stringent criteria and are more than adequate to sterilize or disinfect instruments, devices, or other items contaminated with blood or other body fluids from persons infected with blood-borne pathogens including human immune deficiency virus (HIV) and the hepatitis B virus (HBV). Specifically HBV has been shown to be inactivated by several intermediate- and high-level disinfectants and HIV by a wide range of chemical germicides, even those that are classified as low-level.<sup>2, 5</sup>

The rationale for cleaning, sterilization, and disinfection of bronchoscopes is basically the same as for other critical or semicritical devices. Most protocols require that the bronchoscope be cleaned thoroughly to remove organic material and then be subjected to sterilization (usually ethylene oxide gas) or high-level disinfection. The most widely used chemical disinfectants for endoscopes include several glutaraldehyde and one hydrogen peroxide based formulation. Other formulations should be entering the market in early 1990. Routine high-level disinfection of endoscopes is a safe procedure if done properly and if the manufacturer's guidelines are followed.

## SUMMARY

The effective use of antiseptics, disinfectants, and sterilization procedures in health care settings is important in the prevention of hospital-acquired infections. Sterilization can be accomplished by the steam autoclave, ethylene oxide gas sterilizers, and with EPA-approved chemical sterilants. Devices or items that come into contact with mucous membranes should be sterilized or, at a minimum, re-

ceive high-level disinfection. Chemical germicides that are registered with the EPA as sterilants may be used either for sterilization or for high-level disinfection depending on contact time. Devices that are subjected to disinfection or sterilization procedures should be cleaned before being exposed to a chemical germicide, and the manufacturer's instructions for use of the germicide should be closely followed. Further, it is important that the manufacturer's specifications for compatibility of the medical device with chemical germicides be closely followed. In the specific instance of medical devices used in the field of anesthesiology, current recommendations by the American Society for Anesthesiologists, as well as other professional organizations and the CDC, are sufficient to prevent the transmission of infection from patient to patient and from patient to staff members. None of these classical protocols needs to be changed when these instruments are used on individuals infected with HIV or HBV.

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## **Decontaminating Anesthesia and Respiratory Therapy Equipment**

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The transmission of disease within the hospital is a major problem facing the medical community and the patients served by this community. Nosocomial infections occur in 2 to 15 per cent of patients admitted to general hospitals, and may be more prevalent in tertiary care centers. An estimated 1.5 to 2.5 million people contract hospital-acquired infections and up to 15,000 patients die annually from nosocomial infection.<sup>7</sup> The additional costs in health care and patient morbidity and mortality are enormous.

The equipment used by anesthesiologists and respiratory care specialists is disseminated widely, comes in contact with many patients and workers, and routinely touches mucosal membranes and the respiratory tract. Therefore, we must be aware of our role in the spread of nosocomial infection—a role that has become increasingly important in the face of bacterial resistance to antibacterial agents and of some viral infections that are almost uniformly fatal.

The purpose of this article is to address the role of anesthesia and respiratory therapy equipment in disease transmission and to provide recommendations for cleaning and processing of this equipment.

### **ROLE OF ANESTHESIA EQUIPMENT IN TRANSMISSION OF DISEASES**

#### **History**

The lack of concern for cleanliness among anesthesiologists and the potential role of anesthesia machines as a source of infection or

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cross contamination among patients has been a source of controversy for many years.<sup>4, 25, 53, 70, 98</sup> As early as 1873, Skinner remarked on the relative disregard for cleanliness: "If there be one evil more crying, more disgusting than another in the practice of inducing anesthesia, it is the use of inhalers. . . . There is not one inhaler, my own excepted, where every patient is not made to breathe through the same mouth-piece, tube and chamber . . . sweet seventeen is made to follow a bearded devotee of Bacchus, saturated with the smoke of cigars and the exhalations of Cognac."<sup>31</sup>

Despite this early concern for the repeated use of anesthesia equipment, there was little interest in the potential of the anesthesia apparatus to transmit infectious agents. An editorial in a 1952 edition of the *British Medical Journal* summed up the then current opinion that cases of cross infection were rare and did not justify special precautions except after use on a patient with a known pathogen, for example, *Mycobacterium tuberculosis*.<sup>86</sup> In that same year, Joseph<sup>53</sup> reported the first comprehensive bacteriological survey of anesthesia breathing circuits. He demonstrated that large numbers of organisms inhabited the breathing circuit, and concluded that an outbreak of streptococcal tonsillitis originated from a contaminated anesthetic apparatus. In the following years, the question of infection related to anesthesia equipment was addressed by multiple authors and, by 1964, reflected the change in opinion in a lead article in the *British Journal of Anaesthesia*, which stated "What we really need are the same standards of cleanliness applied to the work of the anaesthetists as to that of the surgeon . . . and a complete change of apparatus for each case. . . . Anaesthetists must be adamant on the question of cleanliness and must insist on facilities for maintaining a good standard in this respect. . . . Only then will they be able satisfy their colleagues who will surely one day inquire closely into the part anaesthetists play in hospital cross-infection. This part may well be bigger than is expected."<sup>21</sup> This concern was also expressed in several other articles written during the 1960s.<sup>65, 72, 85</sup>

Few instances of clinical cross infection have been published since Joseph's original article.<sup>53</sup> In 1967 Tinne reported an outbreak of *Pseudomonas* respiratory infections in a group of patients undergoing cardiac operations.<sup>91</sup> Three patients who received tracheostomies, corticosteroids, and antimicrobial drugs died from their infections. Careful environmental sampling and pyocine typing of isolated strains identified a contaminated anesthesia machine as the probable source of the epidemic. In 1972 Olds et al<sup>70</sup> reported *Pseudomonas* pneumonias in a group of cardiac surgery patients with one resultant mortality. An environmental bacteriologic survey revealed that *Pseudomonas* strains were recovered only from the bellows vent, Y-piece connector, and face mask of the anesthesia machine used for these patients. The epidemic occurred during a 4-month period. Subsequently, autoclave sterilization of all detachable anesthesia equipment stopped the spread of *Pseudomonas* infections. A different ex-

ample of cross infection occurred in a maternity unit where several cases of enteritis were traced to an anesthesia face mask that harbored *Salmonella montevideo*.<sup>79</sup>

### Sources of Contamination

Bacterial or viral contamination of anesthesia equipment may arise from multiple sources. The exterior and interior surfaces of anesthesia machines, monitors, drug carts, and storage compartments are exposed to contamination from used anesthetic equipment, blood, transfused blood products, the surgical field, and personnel.<sup>88</sup> Numerous pieces of anesthesia equipment directly contact mucous membranes, skin, sputum, and other body fluids from the mouth and respiratory tract.

The liberation of pathogenic organisms from patients' airways represents a real and significant problem. Duguid demonstrated that between 0 and 250 bacteria-bearing droplets exit the airway during normal speech, with higher numbers released during forceful speech.<sup>28</sup> In contrast, coughing or sneezing may release 3500 to 1 million bacteria-laden droplets per sneeze or cough from healthy test subjects. The organisms released during these maneuvers primarily originate from the anterior portion of the oropharynx, whereas most respiratory pathogens colonize the nose and posterior pharynx. A study that supported this finding examined three patient groups suffering from streptococcal, diphtheria, or tuberculosis infections where a certain number of patients in each group did produce infected droplets.<sup>27</sup> Large numbers of viruses have been recovered from small particles produced by sneezes and coughs during nonrhinoviral upper respiratory infections.<sup>55</sup> Additionally, the airborne transmission of Coxsackievirus A type 21 and Varicella-Zosters has occurred.<sup>55, 59</sup>

During general anesthesia, patients primarily breath quietly, which releases very few organisms. However, coughing and explosive expirations are not uncommon during emergence and represent one source of the breathing circuit contamination. The aerosols that are chiefly generated in the anterior mouth probably are not formed when the trachea is intubated. However, forcible expulsion of tracheal secretions undoubtedly represents a generous source of organisms for the breathing circuit, especially in patients with tracheal or pulmonary colonization or infection.

### Distribution of Bacteria in Circuits

Consistent with the aerosol source of organism release, those portions of the circuit that are closest to the patient are the most heavily contaminated. These portions include the elbow connector, Y-piece, exhalation valves, breathing tubes, reservoir bag, and ventilator. In 1960 MacCallum and Noble<sup>60</sup> demonstrated that airborne clouds of mixed salivary organisms traversed 3-foot lengths of corrugated tubing. Fifty per cent of the organisms were retained in the tubing, and 50 per cent travelled its length.

Other anesthesia equipment in which micro-organisms have been

observed include endotracheal and tracheostomy tubes, oral and nasal airways, suction catheters, face masks, rebreathing valves, flutter valves, soda lime cannisters, the anesthesia machine working surface, equipment carts, gas tanks, laryngoscope blades, and Magill forceps. The bacterial flora vary little in content throughout the various portions of the circuit; however, the number of organisms and the frequency of contamination varies.<sup>88</sup>

### Bacteriology of Circuits

The vast majority of anesthesia equipment that is used each day is contaminated in some fashion.<sup>88, 89, 97</sup> Known pathogens isolated from anesthetic gas-delivery equipment include *Streptococcus pyogenes*, *Streptococcus viridans*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Mycobacterium tuberculosis*, *Escherichia coli*, *Clostridium perfringens*, *Salmonella montivideo*, *Klebsiella pneumoniae*, pneumococci, *Haemophilus influenzae suis*, and *Candida albicans*. Other organisms that were isolated from breathing circuits include *Staphylococcus albus*, *Micrococcus catarrhalis* and *citreus*, hemolytic and nonhemolytic *Streptococci*, *Neisseria*, *Corynebacterium diphtheriae mitis*, coliform species, *Bacillus subtilis*, *Proteus mirabilis*, *Alcaligenes* species, *Flavobacterium*, *Aspergillus*, *Monilia*, fungi, and yeasts.<sup>97</sup>

To date, there are no reports of viruses or *Mycoplasma* organisms that have been recovered from the anesthetic apparatus. Their potential presence in the circuit remains a major concern because of their wide distribution in patient populations, ease of spread, difficulty to remove, and the potentially dire consequences associated with human infections.

The presence of large numbers of contaminating organisms in parts of anesthesia breathing circuits are easily detected by crude methods such as swabbing. In some cases, bacterial numbers are so large that colonies may be seen. The overwhelming message remains that the potential exists for pathogenic organisms to reside in a high percentage of anesthesia equipment and, therefore, may represent a hazardous reservoir of infection.<sup>65, 94</sup>

### Effects of the Machine Environment on Micro-organism Viability

The interior of the anesthesia circle system is exposed to significant variations in relative humidity, ranging from 70 to 100 per cent during use to approximately 50 per cent during disuse. These shifts together with temperature changes result in inactivation of the vast majority of bacteria within the circuit.<sup>16, 23, 35, 50, 95</sup> Bacterial viability is related inversely to the relative humidity. At relative humidity of 86 per cent, only 1.3 per cent of the original bacterial inoculum remains viable and less than 1 per cent are alive at a relative humidity of 96 per cent. These changes in humidity, temperature, and evaporation act together to limit bacterial viability. Bacterial exposure to most general anesthetic agents affects their survival little.<sup>3, 49, 66, 93</sup> Although oxygen exposure would not appear detrimental to bacterial

survival, this is not the case. Oxygen concentrations as low as 0.01 are lethal to some bacteria when they are suspended in aerosols. Obligate anaerobes die quickly in this environment and do not threaten the anesthetized patient.<sup>13-15, 48</sup>

The anesthesia machine's metal surfaces also provide a hostile environment for bacteria. These metals contain chromium, zinc, and copper. Their ionic forms are oligodynamic and, thus, are extremely toxic in small concentrations to vegetative bacterial cells.<sup>1, 62, 96</sup> Copper's effect is most dramatic in its ability to poison by chelating the actively metabolizing bacterial cell.<sup>1</sup> This property is often utilized in respiratory therapy equipment. Copper mesh or sponges have been inserted into the expiratory limb of the ventilator to prevent bacterial contamination of the intensive care environment.<sup>22, 69</sup>

The factors discussed previously play a significant role in the fact that the anesthesia machine itself has yet to be implicated in a case of cross infection.

### Mode of Transfer from Machine to Patient

The transfer of organisms from breathing circuit to patient occurs in many ways. Equipment that directly contacts the patient's skin, mucous membranes, or bloodstream can transfer micro-organisms readily. However, mode of spread from the interior of a breathing circuit is not so obvious. Several authors claim that the gas flow through the anesthesia apparatus is not capable of pushing organisms out of the circuit.<sup>30, 72</sup> Pandit et al<sup>72</sup> studied the risk of cross infection from inhalation anesthetic equipment in 1967. They specifically addressed the issue of organism transmission by gas flow in an artificially contaminated circuit. An apparatus consisting of a reservoir bag, a corrugated tube with expiratory valve, a catheter mount, and an endotracheal tube connector was artificially contaminated with a known organism, and then connected via sterile tubing to three sterile flasks containing sterile nutrient broth. A nitrous oxide/oxygen gas mixture was passed through the circuit at 8 l per minute and the reservoir bag was intermittently compressed for 30 minutes. There were no viable organisms recovered from any of the sterile broth solutions after exposure. A similar study done in 1977 by du Moulin and Saubermann<sup>30</sup> also revealed minimal contamination in circuits initially presented with a bacteria load, making aerosol spread of bacteria within the anesthesia apparatus unlikely. In contrast, in 1964, Jenkins and Edgar<sup>52</sup> showed that a small proportion of organisms were caught up in the gas stream and, therefore, could be inhaled by the patient.

Another mode of transfer is related to the large amount of water that is often present within the circuit. Condensation derived from the patient's exhaled gases may pick up organisms. This contaminated liquid can flow into the patient's airway if the circuit is above the level of the patient's face. Finally, the anesthesiologist contributes organisms to the circuit because his hands and clothing often contact infected surfaces, especially if the anesthesiologist does not practice good personal hygiene.

### Risk of Cross Infection from Anesthesia Equipment

The risk of cross infection from anesthesia equipment remains controversial. Stark and coworkers<sup>55</sup> wrote the following statements in their 1962 article: "Having regard to the numbers of organisms recovered from anaesthetic machines infected under conditions approximating those found in clinical practice, it appears that infection is unlikely to be transmitted from patient to patient. . . . Where a patient is known to be infected with a virulent organism such as *M. tuberculosis* or an antibiotic-resistant *S. aureus*, we consider that anaesthesia should be conducted with apparatus which can easily be sterilized after use, and be kept exclusively for this purpose."

This opinion is shared by others.<sup>30, 72</sup> Several recent studies examine the role of bacterial filters in the anesthesia circuit to prevent postoperative pneumonia.<sup>42, 44</sup> They concluded that the use of bacterial filters did not contribute to improved patient outcome, and that the financial resources used to purchase these devices could be spent better elsewhere. Mazze,<sup>64</sup> in his accompanying editorial, states: "If these devices are not clinically efficacious, then at the least, their use introduces an unnecessary expense into anesthesia practice. At the most, their use may be associated with complications which can be more serious than the disease they are intended to prevent."<sup>11</sup>

Other authors take the opposite position. Dryden<sup>24</sup> recommends that anesthesiologists establish a rigid clean-up program between each patient. Based on his research, Thomas<sup>89</sup> considered the risk of cross infection to be sufficiently high that every patient should be ventilated with a new, sterile circuit.

The transmission of viral infections in the hospital setting is common<sup>46, 92</sup> and may manifest as a single subclinical infection or a large epidemic. The viruses of most concern to anesthesiologists and their patients include hepatitis B, herpesvirus, respiratory syncytial virus, adenovirus, influenza/parainfluenza virus, rhinovirus, rubella virus, Creutzfeldt-Jakob disease, and human immunodeficiency virus (HIV). At present, no published study attempts to determine the fate of viral particles expelled into the anesthesia machine. The various conditions of humidity, desiccation, and temperature all influence their survival. In general, viruses cannot survive for long periods outside a viable host. However, hepatitis B, rhinoviruses, and others may remain dormant on inanimate surfaces for weeks at room temperature.<sup>29, 36, 47, 87</sup> Influenza virus can survive for 24 hours within an anesthesia circuit, although survival depends on relative humidity.<sup>32</sup> Finally, oral transmission and possible person-to-person transmission of the slow brain viruses has been demonstrated.<sup>26, 44</sup>

Because of their small size, hepatitis B and other viruses pass through filters with 52 nm pores.<sup>78</sup> These viruses' small size also enhances airborne transmission. Particles that are 1 to 3 nm in diameter may remain suspended almost indefinitely, especially if occasionally elevated by air currents. The study by Favero et al<sup>36</sup> demonstrated minimal loss of hepatitis B virus antigenicity in constant conditions

of ambient environment. The indefinite, airborne suspension of hepatitis B virus along with its antigenic stability makes the potential for airborne spread real. However, these are primarily blood-borne infections, and there is no evidence that either HBV or HIV is transmitted by airborne routes or by aerosols from the respiratory tract. Furthermore, despite known airborne transmission of other viruses similar in size to hepatitis B, no data to substantiate or refute this theory of cross infection with regard to the anesthesia machine have been gathered.<sup>56</sup>

### CROSS INFECTION FROM RESPIRATORY THERAPY EQUIPMENT

In contrast to anesthesia machines, cross infection due to respiratory care equipment has been well documented.<sup>34, 67, 68, 73, 76, 77</sup> The risks and mechanisms of cross infection are similar to those of the anesthesia machine; direct contact with the bloodstream when vascular integrity has been compromised, skin, or mucous membranes and dissemination by contaminated aerosols.

#### Resuscitation Bags

Resuscitation bags have been implicated as the source of several bacterial epidemics. An outbreak of *Pseudomonas aeruginosa* in an intensive care unit was traced to a heavily contaminated self-inflating breathing bag.<sup>9</sup> Another *Pseudomonas aeruginosa* epidemic was traced to a delivery-room resuscitator. This epidemic involved 22 infants and resulted in two mortalities.<sup>39</sup> Finally, a recent article that reviewed resuscitation bags with constantly flowing oxygen as a source of bacterial contamination found that 75 per cent of the valves and 25 per cent of the aerosols produced by bags were bacteria-laden.<sup>90</sup>

#### Nebulization Equipment

Nebulization equipment frequently has caused nosocomial pneumonias.<sup>67, 68, 73, 76, 77</sup> A study from Parkland Memorial Hospital demonstrated a tenfold increase in the incidence of gram-negative necrotizing pneumonia during the period 1952 to 1963, corresponding to the increased use of nebulization equipment.<sup>73</sup>

Large-volume nebulizers with reservoirs greater than 500 ml and ultrasonic nebulizers present the greatest risk to the patient.<sup>20</sup> Small-volume Venturi-type medication nebulizers that are used to administer medications pose relatively little infectious risk. When these nebulizers are contaminated, the source is usually multidose medication vials.<sup>80</sup> Nebulization equipment also produces environmental contamination and may be a source of cross contamination between patients. Bacteria can travel up to 32 feet beyond the exhalation valve of an intermittent positive pressure breathing (IPPB) machine.<sup>33</sup> These re-

sults were corroborated in a study using a canine model of *Pseudomonas aeruginosa* pneumonia, which demonstrated that the organism could be recovered at distances up to 15 feet.<sup>12</sup>

### Mechanical Ventilators with Humidifiers

The current Centers for Disease Control guidelines for prevention of nosocomial pneumonia recommend that mechanical ventilator breathing circuits should be changed every 24 hours.<sup>81</sup> Other literature suggests that this period may be extended safely to 48 hours, but length of time to contamination depends highly on the type of ventilator circuit that is employed.<sup>6, 16, 57</sup> Lareau et al<sup>57</sup> demonstrated no differences in bacterial numbers cultured from the inspiratory gas of patients experiencing circuit changes every 8, 16, and 24 hours. Craven et al<sup>16, 18</sup> reported no difference in inspiratory gas bacterial levels from patients with 24- and 48-hour circuit changes. In contrast to the previously quoted adult studies, Malecka-Griggs assessed 24- and 48-hour changes of semiclosed disposable circuits in a Neonatal Intensive Care Unit.<sup>61</sup> She reported a significant decrease in the circuit contamination rate when circuits were changed every 24 hours, rather than every 48 hours. Thus, frequent circuit changes reduced colonization and cross infection in the neonatal population. Although circuit changes every 48 hours have been questioned in the neonatal population, they appear to be justified in the adult population, and can result in a considerable cost savings.

### Ventilator Tubing

Mechanical ventilators with heated humidifiers frequently have significant tubing colonization and condensate formation. As expected, bacterial concentrations are highest near the patient with little colonization detected in the distal tubing or humidifier.<sup>17, 45</sup> The bacterial concentration of the condensate is high and contains gram-negative rods in the vast majority of isolates.<sup>20</sup> Simple, clinical procedures may cause the contaminated condensate to flow directly into the tracheobronchial tree. At present no cause-and-effect relationship between tubing colonization and nosocomial pneumonia has been demonstrated; however, the potential risk exists. Furthermore, tracheobronchial inoculation with large volumes of fluid containing high bacterial concentrations is an effective way to overcome pulmonary defense systems and produce pneumonia in laboratory animals.<sup>71</sup>

An alternative approach to contamination control during long-term mechanical ventilation employs a heat-and-moisture-exchanging bacterial filter (HME).<sup>40</sup> Gallagher and coworkers<sup>40</sup> studied 28 patients using a Pall Ultipor Breathing System Filter (Pall Biomedical, Fajardo, Puerto Rico) as a heat- and moisture-exchanging bacterial filter. They concluded that the filters provided an efficient, in vivo bacterial barrier and prevented the contamination of respiratory apparatus with human pathogens. Use of these filters obviated the need to sterilize breathing systems or decontaminate ventilators. Further, in low-flow ventilator systems, they performed satisfactorily as heat

and moisture exchangers and offered substantial advantages in cost, ease of use, and patient safety. However, because this is only a single study plus the increased resistance that these filters introduce, clinical acceptance of replacing humidifiers with micropore filters has been slowed.

### In-Line Medication Nebulizers

In-line nebulizers may become contaminated with large numbers of organisms.<sup>19</sup> The organisms are usually the same as those present in the tubing condensate, suggesting condensate influx as a possible source. Because of their low volumes and their relatively infrequent use, these nebulizers probably pose a small risk for pneumonia. However, nebulizers that are removed from the circuit should be used with sterile liquid and should be dried between uses. This procedure is probably superior to the use of a new nebulizer every 24 hours.<sup>20</sup>

### Humidifier Colonization

Cultures of cascade humidifiers after 24 and 48 hours of use demonstrated no growth in 88 per cent of the samples and only low levels of colonization in the remaining 12 per cent. In vitro studies demonstrated that many nosocomial pathogens are killed by heat. Thus, colonization of bubble-through humidifiers is low and represents an unlikely source of infection.<sup>20, 45</sup>

### Spirometers and Oxygen Analyzers

Spirometers and oxygen analyzers have been implicated in the transfer of *Acinetobacter* and *Pseudomonas maltophilia* infections in two published reports.<sup>10, 51</sup> Because of their potential exposure to bacterial contamination from the ventilator circuit, they should not be used in sequential patients until they are disinfected.<sup>20</sup>

## DECONTAMINATION OF EQUIPMENT

The term decontamination refers to the reduction of microbial contamination to some acceptable level. This may range from a mild reduction in microbial count to complete ablation of all life forms or infective agents. The following is a series of brief definitions: (1) Cleaning is the process of removing foreign material such as blood, sputum, and dust from objects. It is an essential preliminary procedure intended to improve the access of germicides that are applied subsequently to any remaining contaminants.<sup>11</sup> (2) Disinfection refers to killing pathogenic organisms on inanimate objects. Spalding<sup>52</sup> further subdivides this process into three levels: high, intermediate, and low. If exposure times are sufficient, high-level disinfectants are capable of sterilizing all bacteria, fungi, and viruses.<sup>51</sup> (3) Sterilization is a process that completely destroys all microbial life. The rationale for decontaminating medical equipment is based on the perceived risk

that exposure to the equipment poses to patients. Medical equipment is classified into three categories based on decontamination need: critical, semicritical, and noncritical.<sup>43</sup> Critical items are those that enter the bloodstream or other areas of the body by penetrating skin or mucous membranes. These items must be sterile at the time of insertion.

Semicritical items are those that contact intact mucous membranes. It is not essential that these devices be sterilized; however, Spector<sup>83</sup> stated that all endoscopes used on patients suspected of having hepatitis B or HIV must be gas sterilized.<sup>31</sup> At a minimum, these instruments should undergo a high-level disinfective process. Noncritical items are those that touch only intact skin or do not touch the patient at all. In general, the intact skin is an effective barrier to most micro-organisms, thus necessitating only cleanliness. However, justification for routine low- or intermediate-level disinfection becomes difficult in light of the availability of inexpensive and efficient germicidal agents.

### RECOMMENDATIONS FOR DECONTAMINATION OF ANESTHESIA EQUIPMENT

1. All reusable portions of the breathing circuit that directly contact the patient or that may be contaminated by sputum or other organic materials should be washed and sterilized, or subjected to appropriate disinfection between patients.<sup>37</sup> If these procedures are not feasible, then the use of disposable circuits and facemasks is recommended.

2. Used laryngoscopes and other nondisposable overtly contaminated items should remain separate from clean equipment. They should be washed with detergent and water and undergo either high-level disinfection or sterilization between patients.

3. Suction catheters should be single-use sterile items because of the difficult, time-consuming cleaning procedures that they require.

4. Carbon dioxide absorbers should be cleaned and disinfected when the soda lime is changed. Unidirectional valves also should be cleaned at this time. Single-use absorbers are available.<sup>10</sup>

5. Anesthesia ventilators are an extension of the breathing bag in the anesthetic circuit and are contaminated frequently. Only equipment that can be disassembled should be purchased, and regular cleaning and high-level disinfection or sterilization is recommended.<sup>75</sup>

6. Bacterial filters on the inspiratory and expiratory limbs of the breathing circuit protect the machine from direct contamination by bacteria; however, in prospective studies they do not reduce the incidence of postoperative pneumonia.<sup>38, 74</sup> Bacterial filters have been recommended for use in conjunction with disposable circuits for patients with active hepatitis B infections<sup>29</sup> despite the lack of evidence that this is an effective or necessary precaution. A study by Ball et al<sup>2</sup> has demonstrated that the Pall HME filter is able to capture bacteriophages. An HME filter routinely used between the elbow and the circuit may become part of "universal contamination precautions."

7. Self-inflating breathing bags should be disassembled, cleaned, and either high-level disinfection or sterilization techniques used between patients. Disposable, single-use self-inflating breathing bags are available.<sup>75</sup>

8. The exterior surface of the anesthesia machine, monitors, and equipment carts should be cleaned at least every 24 hours and whenever visibly contaminated. A chemical germicide that is registered with and approved by the Environmental Protection Agency as a "sterilant" should be used. Sterilants may be used for sterilization or for high-level disinfection, depending on contact time. Germicides that are approved for use as "hospital disinfectants" and that are tuberculocidal when used at appropriate dilutions may be used for high-level disinfection of devices and instruments. Germicides with tuberculocidal activity are preferred because mycobacteria are some of the most resistant organisms. Germicides effective against mycobacteria are also effective against most other bacterial and viral pathogens.<sup>58</sup> Another alternative is to use a 1:100 or 1:1000 dilution of bleach, which is effective against HIV.<sup>63, 84</sup> In cases involving Creutzfeldt/Jakob disease, 0.5 to 1 per cent bleach has been recommended<sup>5, 41</sup> for at least 1 hour.<sup>8</sup>

9. Equipment that contacts only intact skin, such as blood pressure cuffs and tubing, headstraps, and pulse oximeters, should be cleaned after each use.<sup>75</sup>

### RECOMMENDATIONS FOR RESPIRATORY THERAPY EQUIPMENT

1. All portions of the circuit that have direct contact with the patient's airway or that may be contaminated by sputum or other organic materials should be washed and sterilized between patients. If these procedures are not feasible, then disposable circuits should be used.

2. The frequency of ventilator circuit and humidifier changes is controversial and depends highly on the types of circuits and humidifiers that are employed. The most recent CDC guidelines suggest changing this equipment every 24 hours.<sup>81</sup> Numerous published reports advocate 48-hour intervals.<sup>6, 16, 57</sup> Finally, an efficient heat-and-moisture-exchanging bacterial filter can be used to maintain circuit/machine sterility and may eliminate the need for a humidifier.<sup>40</sup>

3. Suction catheters should be single-use, sterile items.

4. Environmental surfaces of the machines should be cleaned with a disinfectant having tuberculocidal and viricidal activity at least every 24 hours and whenever visibly contaminated.

5. Self-inflating breathing bags should be disassembled, cleaned and undergo either high-level disinfection or sterilization between patients.<sup>75</sup> Disposable breathing bags are available.

6. After each patient, the ventilator should be washed entirely with an appropriate disinfectant solution, and disassembled; all filters and accessory equipment should be removed and either sterilized or replaced if disposable.

7. All other reusable equipment, for example, nebulizers, laryngoscopes blades, and goggles, should be sterilized between uses.

### CONCLUSION

Undoubtedly, with patient use, the anesthesia and respiratory care equipment becomes contaminated. The resultant risk of cross-infection to subsequent patients varies depending on the equipment's

function, the proximity of the patient to the equipment, the resistance of the contaminating organism, the equipment environment's effect on the organism, and the type of exposure subsequent patients have to contaminated equipment. At present, the risk from anesthesia equipment that is properly treated appears low. The few cases in which the machine or breathing circuit have been implicated have involved *Pseudomonas* species. Further, no clinical studies document the machine's ability to cause infection.

The role of respiratory therapy equipment in bacterial cross-infection has been well documented, especially with regard to several commonly used pieces of equipment. The frequency with which circuit changes should be made remains controversial; however, the best intervals are probably every 24 to 48 hours, depending on the type of circuit and humidifier in use. The role of respiratory therapy equipment in the transmission of viral infections remains unstudied.

Thus, we are faced with a series of important, unanswered questions: (1) What is the specific role of the anesthesia machine in the transmission of viral infections? (2) Are current recommendations for routine care of anesthesia and respiratory therapy equipment appropriate for use in all patients? If not, what "universal precautions" should be implemented to prevent contamination of the anesthesia machine and infectious transmission to patients or health care providers? (3) What role does respiratory therapy equipment play in the transmission of viral infections?

Our ability to answer these questions and to propose effective solutions seems more pressing in light of deadly and virulent viral and mycobacterial infections that patients unknowingly carry to our equipment.<sup>54</sup> Also, anesthesiologists are caring for immunocompromised patients more often, and this group may be unable to protect themselves against what formerly were thought to be harmless environmental organisms or insignificant inoculums. Therefore, we must remain consistent in our attempts to deliver state-of-the-art care in a time- and cost-conscious environment. Prospective, controlled studies to address these questions must be pursued.

## SUMMARY

This article reviews the history and documents the role played by anesthesia and respiratory therapy equipment in infection control. The role of the anesthesia machine in cross-infection is controversial. There is no question that the machine may become contaminated; however, infection has been traced only to contaminated equipment that directly contacts patients. Therefore, the machine poses a small risk for cross-infection.

Respiratory therapy equipment has been implicated in numerous cases of cross-infection. Sterile, disposable, or sterilized reusable equipment for each patient has reduced the cross-infection incidence. Despite current recommendations by the CDC, current state of adult

practice supports changing breathing circuits on ventilators every 48 hours.

The possibility of viral infection remains a concern despite the absence of any documented transmission of viral infections related to the anesthesia machine or respiratory therapy equipment. Major questions remain unanswered regarding appropriate safeguards.

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## **Infection Control in Anesthesia**

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Every anesthesia department should have an infection control plan that documents procedures and policies to prevent transmission of infectious agents to patients during their anesthetic care and to minimize exposure of anesthesia personnel to occupational infectious hazards. The former aspect of infection control is a part of providing safe anesthesia and is included in departmental quality assurance programs. Some of these topics have been covered in other articles in this issue and will be touched on in part in this article. Most hospitals have infection control practitioners who work with an infection control committee to help to formulate, institute, and monitor infection control plans.

The general duty clause of the Occupational Safety and Health Act of 1970 requires employers to provide employment and a place of employment that are free from recognized hazards. The Occupational Safety and Health Administration (OSHA) of the federal government has determined that some health care workers face a significant risk for infections, especially blood-borne infections, as a result of their employment. This risk can be minimized or eliminated by educating health care workers on specific work practices and protective clothing and providing vaccination and medical follow-up of known exposures. OSHA has proposed Federal standards of practice to reduce employees' risk of blood-borne infections. A part of these standards are the "universal blood and body fluid precautions" or "universal precautions" that had been recommended by the Centers for Disease Control (CDC). Because of the frequent contact with blood and body fluids, anesthesia personnel are a group at high risk for occupational exposure to blood-borne pathogens such as hepatitis B virus (HBV) and the human immunodeficiency virus (HIV).

### **OCCUPATIONAL TRANSMISSION OF BLOOD-BORNE INFECTIONS TO HEALTH CARE WORKERS**

Several surveillance studies have demonstrated that the risk of hepatitis B is greater than for HIV infection for health care workers

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with frequent blood exposure. In the United States, almost 20 per cent of anesthesiologists were seropositive for HBV markers in a multicenter study performed in academic institutions.<sup>3</sup> This is in contrast to the very low risk of occupational transmission of HIV infection to health care workers.<sup>7</sup> In one case report, HBV but not HIV was transmitted through an accidental needle-stick from a patient infected with both viruses.<sup>17</sup> The number of infectious units in the blood of a HBV carrier is significantly greater than that found with HIV, which results in a greater risk of HBV infection after a parenteral exposure.

There are now several prospective surveillance studies following health care workers who have been exposed to blood or body fluids from HIV-positive patients. The largest of these studies, the CDC Cooperative Needle-Stick Surveillance Group, includes more than 1200 health care workers.<sup>22</sup> In this series, more than 80 per cent of health care workers had parenteral (piercing the skin barrier) exposures. There were four seroconversions for HIV antibody, constituting a seroprevalence rate of 0.42 per cent. Of particular note is the fact that 37 per cent of the needle-stick injuries reported in this series could have been prevented if the health care worker had carefully adhered to suggested infection-control procedures. Similar studies from the National Institutes of Health<sup>19</sup> and San Francisco General Hospital<sup>16</sup> also documented a low risk of seroconversion for exposed health care workers. From these prospective studies, it appears that the greatest risk for HIV infection follows parenteral exposures to blood from HIV-infected patients and that the risk of seroconversion is less than 1 per cent and probably about 0.5 per cent.<sup>7, 22</sup>

In addition to the prospective studies, there have been ten case reports of health care workers with documented HIV seroconversion after parenteral or other exposure to HIV-infected blood as a result of patient care activities or from exposure in a clinical or research laboratory. Upon investigation, these individuals denied nonoccupational risk factors for HIV infection.<sup>7</sup> There are reports of at least six other health care workers with HIV infection who have no apparent nonoccupational risk factors but the time of seroconversion was not documented.

## **PRECAUTIONS TO PREVENT TRANSMISSION OF BLOOD-BORNE INFECTIONS**

### **Universal Precautions**

Since blood and body fluids from infected patients are capable of transmitting infectious agents (HBV, HIV, non-A, non-B hepatitis, malaria, and so forth), the CDC has recommended procedures for use by health care workers who have contact with these substances.<sup>5-7</sup> These blood and body fluid precautions should be used consistently for all patients since the infection status of patients may be unknown.<sup>2</sup> This approach is referred to as "universal precautions," and this in-

cludes use of barriers to prevent skin and mucous membrane exposure to blood and body fluids and precautions to prevent injuries caused by needles and other sharp objects.<sup>4</sup>

1. "All health care workers should routinely use appropriate barrier precautions to prevent skin and mucous membrane exposure when contact with blood or other body fluids of any patient is anticipated. Gloves should be worn for touching blood and body fluids, mucous membranes, or non-intact skin of all patients, for handling items or surfaces soiled with blood or body fluids, and for performing venipuncture and other vascular access procedures. Gloves should be changed after contact with each patient. Masks and protective eye wear or face shields should be worn during procedures that are likely to generate droplets of blood or other body fluids to prevent exposure of mucous membranes of the mouth, nose, and eyes. Gowns or aprons should be worn during procedures that are likely to generate splashes of blood or other body fluids."<sup>4</sup>

Several types of medical gloves are marketed including sterile surgical or nonsterile examination gloves made of vinyl or latex. There are no reported differences in barrier effectiveness between intact latex and intact vinyl gloves, and therefore, the type used should be appropriate for the task and allow adequate manual dexterity.<sup>9</sup> Sterile gloves should be used for procedures involving contact with sterile areas of the body. Examination gloves can be used for procedures in which sterility is not required and the purpose of the glove is to prevent transmission of infection from the patient to the health care worker.

The CDC has updated its recommendation on the use of gloves during phlebotomy. It is recognized that gloves cannot prevent penetrating injuries caused by needles used during phlebotomy. The likelihood of skin contamination with blood during phlebotomy depends on the skill and technique of the health care workers and the experience that they have had with the procedure. Although gloves should always be made available to health care workers who wish to use them for phlebotomy, some institutions feel that gloves are not necessary at all times for phlebotomy. Gloves should be used if the health care worker has cuts or other breaks in the skin, as well as when contamination with blood may occur during phlebotomy as on an uncooperative patient. Inexperienced individuals should use gloves during training in phlebotomy.<sup>9</sup> These recommendations do not apply for health care workers inserting intravenous catheters in which the likelihood of skin contamination with blood is much greater.

Many products have been devised as barriers to prevent splashes of blood contacting the eyes or mucous membranes of the mouth. These consist of protective eye wear or face shields (Fig. 1). Based on the anticipated degree of exposure, professional judgment must be used to determine the appropriate barriers to be worn during procedures.

2. "Hands and other skin surfaces should be washed immediately and thoroughly if contaminated with blood or other body fluids. Hands should be washed immediately after gloves are removed."<sup>9</sup>



Figure 1. Face shields may be worn instead of eye-glasses or goggles when extensive splashing of blood or body fluid is anticipated. These will protect both the eyes and mucous membranes of the mouth and nose. (Anti-infection Shield, Stackhouse Associates, Inc., El Segundo, CA.)

Handwashing is one of the primary infection control measures. It is often impractical for anesthesia personnel to immediately leave the operating room during an anesthetic to wash their hands. Therefore, the primary goal should be to prevent accidental blood contact through the use of barriers. Between patients and at other convenient times, anesthesia personnel should wash their hands.

3. "All health care workers should take precautions to prevent injuries caused by needles, scalpels, and other sharp instruments or devices during procedures; when cleaning used instruments; during disposal of used needles; and when handling sharp instruments after procedures. To prevent needle-stick injuries, needles should not be recapped, purposely bent or broken by hand, removed from disposable syringes, or otherwise manipulated by hand. After they are used, disposable syringes and needles, scalpel blades, and other sharp items should be placed in puncture-resistant containers for disposal; the puncture-resistant containers should be located as close as practical to the use area."<sup>4</sup>

Needles are frequently used during anesthesia for the administration of medication, performing lumbar punctures and regional anesthetics, and inserting intravenous and intra-arterial catheters. Particular care must be taken to prevent accidental needle-sticks because parenteral exposures are the most likely to transmit blood-borne infections. The CDC recommendations do not differentiate between needles that are contaminated with blood and needles that have been used to draw up sterile medication for administration into intravenous tubing.

Industry is working actively to devise equipment that will prevent accidental needle-sticks (Figs. 2 and 3). Some anesthesiologists are

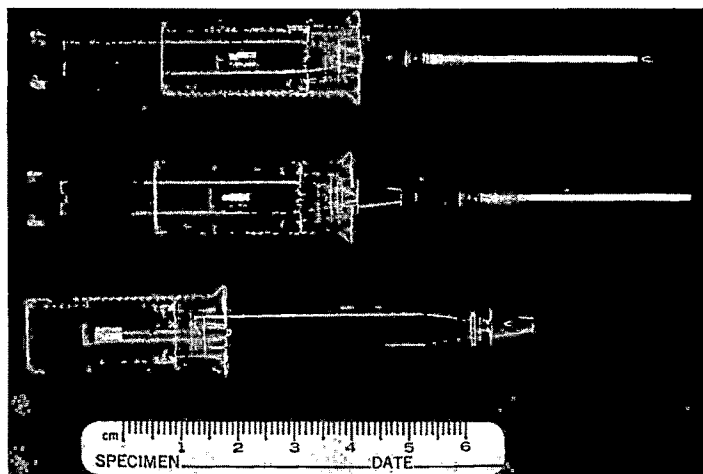


Figure 2. As this intravenous catheter is inserted, the needle is covered by a rigid plastic sheath that locks into place (*bottom*). (Protectiv IV, Critikon Inc., Tampa, FL.)

using stopcocks in intravenous tubing to administer drugs in an effort to diminish the use of needles in their practice. Other solutions for this problem will be forthcoming.

4. "Although saliva has not been implicated in HIV transmission, to minimize the need for emergency mouth-to-mouth resuscitation, mouthpieces, resuscitation bags, or other ventilation devices should be available for use in areas in which the need for resuscitation is predictable."<sup>4</sup>

5. "Health care workers who have exudative lesions or weeping der-

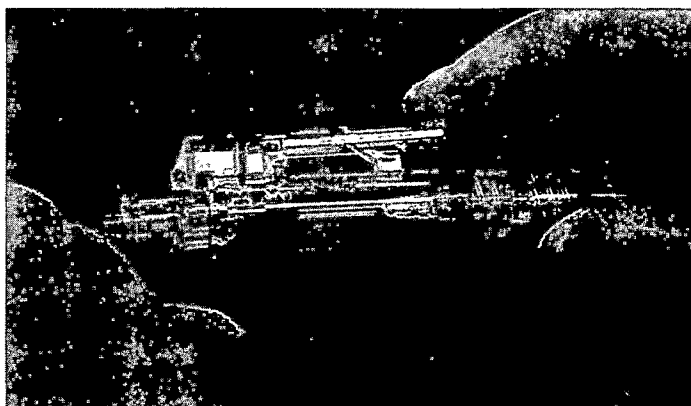


Figure 3. The needle on the intravenous infusion set is protected by a rigid plastic cylinder that allows it to be inserted into the injection site without the risk of an accidental needle stick. (Click Lock Needle Housing and Injection Site, ICU Medical, Inc., Huntington Beach, CA.)

matitis should refrain from all direct patient care and from handling patient-care equipment until the condition resolves.”<sup>4</sup>

6. “Pregnant health care workers are not known to be at greater risk of contracting HIV infection than health care workers who are not pregnant; however, if a health care worker develops HIV infection during pregnancy, the infant is at risk of infection resulting from perinatal transmission. Because of this risk, pregnant health care workers should be especially familiar with and strictly adhere to precautions to minimize the risk of HIV transmission.”<sup>4</sup>

### **CDC Update on Universal Precautions**

The CDC has clarified the recommendations for universal precautions as a result of questions raised by practitioners.<sup>9</sup> In the community, blood-borne pathogens are transmitted to persons through sexual activity, infected blood by sharing needles during intravenous drug administration, and perinatally from mother to child, whereas in the occupational setting, blood is the single most important source for transmission. HBV and HIV have been isolated from many body fluids, but not all have been associated with transmission of infection. Universal precautions should be used with all body tissues, and pertains to the following body fluids: cerebrospinal fluid, synovial fluid, pleural fluid, peritoneal fluid, pericardial fluid, amniotic fluid, semen, and vaginal secretions. Because the associated risk of transmission of HIV and HBV is extremely low or nonexistent, universal precautions do not apply to feces, nasal secretions, sputum, sweat, tears, urine, and vomitus unless they contain visible blood. Human breast milk has been implicated in perinatal transmission of HIV, and hepatitis B surface antigen has been found in the milk of mothers infected with HBV. Occupational exposure to this fluid has not been implicated in the transmission of these infections to health care workers.

Saliva from HBV carriers may be hepatitis B surface antigen positive,<sup>29</sup> but has not been shown to be infectious when applied to oral mucous membranes or injected into experimental animals.<sup>26</sup> Universal precautions do not apply to saliva unless it contains visible blood, which may be the case with trauma from endotracheal intubation or pharyngeal suctioning. Because other pathogens such as herpes virus may be transmitted in oral secretions, general infection control practices include the use of gloves whenever saliva and oral mucous membranes are contacted. Therefore, gloves should be worn during endotracheal intubation, oral pharyngeal suctioning, inserting or removing nasogastric tubes, during bronchoscopy or fiberoptic laryngoscopy, and for patient extubation. After completion of these procedures, contaminated gloves should be removed prior to touching the surface of the anesthesia equipment. Additionally, hands should be washed as soon as possible after glove removal.

## **EQUIPMENT AND ENVIRONMENTAL CONSIDERATIONS**

### **Sterilization and Disinfection of Anesthesia Equipment**

Currently recommended standard sterilization and disinfection procedures for patient care equipment are adequate for instruments

and devices contaminated with blood or body fluids from persons infected with blood-borne pathogens including HIV.<sup>9, 12, 15</sup> As described in the article by Dr. Favero in this issue, instruments or devices that enter sterile tissue or the vascular system of any patient should be sterilized before use, and devices that contact intact mucous membranes should be sterilized or receive high-level disinfection. Rutala<sup>24</sup> has summarized data from multiple sources on methods of sterilization and disinfection (Tables 1, 2, and 3). Chemical germicides that are registered with the United States Environmental Protection Agency as "sterilants" can be used for either sterilization or high-level disinfection depending on contact time.<sup>9</sup> HIV is rapidly inactivated after exposure to commonly used chemical germicides. Disinfectants and other procedures that are classified as tuberculocidal are adequate for inactivation of HBV (Table 2).

The Association of Operating Room Nurses has published recommended practices for cleaning and processing anesthesia equipment.<sup>23</sup> The care of anesthesia equipment has been included in published guidelines by Simmons and Wong.<sup>27</sup> The controversy on the role of the anesthesia machine as a source of infections for patients has been reviewed by Rosenquist and Stock in an article in this issue.

In general, it is best to follow specific manufacturers' instructions for acceptable germicides and decontamination procedures for use with instruments such as fiberoptic laryngoscopes. Use of an inappropriate chemical could damage the instrument or may be insufficient to produce adequate disinfection. With all equipment, it is important to thoroughly clean all surfaces by scrubbing to remove organic material such as dried blood or sputum prior to exposure to germicide. A thick coating of an organic contaminant will prevent the disinfectant from reaching the surface of the equipment and may result in inadequate pathogen inactivation.

Because laryngoscopes and anesthesia face masks contact mucous membranes, they should receive high-level disinfection prior to use. Endotracheal tubes should be sterilized or purchased sterile from the manufacturer because they enter normally sterile body cavities.

### **Reuse of Disposable Equipment**

Some individuals or departments may reuse devices intended by the manufacturer to be for single patient use only. This may require that devices be sterilized or disinfected prior to reuse. Chemicals or processes used for disinfection may damage or weaken the integrity of the product or its components and cause it to malfunction during use. Reuse of disposable devices shifts the product liability from the manufacturer to the individual. Guidelines for the reuse of disposable medical devices have been published, and there are several reviews on the subject.<sup>1, 18</sup> Although this practice may be advantageous economically, there are many legal and ethical ramifications that need to be considered. Quality assurance programs and policies need to be formulated by departments that reuse disposables to ensure that dis-

Table 1. *Methods of Sterilization and Disinfection*

| OBJECT                                  | DISINFECTION                                                                                                |                                                                                      |                                                                          |
|-----------------------------------------|-------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|--------------------------------------------------------------------------|
|                                         | HIGH-LEVEL—SEMICRITICAL                                                                                     |                                                                                      | LOW-LEVEL—NONCRITICAL<br>ITEMS: WILL COME IN<br>CONTACT WITH INTACT SKIN |
|                                         | STERILIZATION—CRITICAL<br>ITEMS: WILL ENTER TISSUE OR<br>VASCULAR SYSTEM OR BLOOD<br>WILL FLOW THROUGH THEM | ITEMS: WILL COME IN<br>CONTACT WITH MUCOUS<br>MEMBRANE OR SKIN THAT IS<br>NOT INTACT |                                                                          |
|                                         | Procedure*                                                                                                  | Exposure<br>time (hr)†                                                               | Procedure (exposure<br>time ≤10 min)                                     |
| Smooth, hard surface                    | A                                                                                                           | Mfr rec                                                                              | C                                                                        |
|                                         | B                                                                                                           | Mfr rec                                                                              | D                                                                        |
|                                         | C                                                                                                           | 10                                                                                   | E                                                                        |
|                                         | D                                                                                                           | 6                                                                                    | F                                                                        |
|                                         | E                                                                                                           | 6                                                                                    | G                                                                        |
| Rubber tubing and catheters‡            |                                                                                                             |                                                                                      | I                                                                        |
|                                         | A                                                                                                           | Mfr rec                                                                              | C                                                                        |
|                                         | B                                                                                                           | Mfr rec                                                                              | D                                                                        |
|                                         | C                                                                                                           | 10                                                                                   | E                                                                        |
|                                         | D                                                                                                           | 6                                                                                    | F                                                                        |
| Polyethylene tubing and<br>catheters‡,§ | E                                                                                                           | 6                                                                                    |                                                                          |
|                                         | A                                                                                                           | Mfr rec                                                                              | C                                                                        |
|                                         | B                                                                                                           | Mfr rec                                                                              | D                                                                        |
|                                         | C                                                                                                           | 10                                                                                   | E                                                                        |
|                                         | D                                                                                                           | 6                                                                                    | F                                                                        |
|                                         | E                                                                                                           | 6                                                                                    | I                                                                        |
|                                         |                                                                                                             |                                                                                      | H<br>J<br>K<br>L<br>M                                                    |

## Lensed instruments

|   |         |   |
|---|---------|---|
| B | Mfr rec | C |
| C | 10      | D |
| D | 6       | E |
| E | 6       |   |

Thermometers (oral and rectal)<sup>||</sup>

I

## Hinged instruments

|   |         |   |
|---|---------|---|
| A | Mfr rec | C |
| B | Mfr red | D |
| C | 10      | E |
| D | 6       |   |
| E | 6       |   |

\* *Procedure A*, Heat sterilization, including steam or hot air (see manufacturer's recommendations); *B*, ethylene oxide gas (see manufacturer's recommendations); *C*, glutaraldehyde-based formulations (2 per cent). A glutaraldehyde-phenate formulation at full-strength also has been shown to sterilize items which are soaked for 6¼ hr. Caution should be exercised with all glutaraldehyde formulations when further in-use dilution is anticipated; *D*, demand release chloride dioxide (will corrode aluminum, copper, brass, series 400 stainless steel and chrome with prolonged exposure); *E*, 6 per cent stabilized hydrogen peroxide (will corrode copper, zinc, and brass); *F*, wet pasteurization at 75°C for 30 minutes after detergent cleaning<sup>†</sup>; *G*, sodium hypochlorite (1000 ppm available chlorine) (will corrode metal instruments); *H*, ethyl or isopropyl alcohol (70 to 90 per cent); *I*, ethyl alcohol (70 to 90 per cent); *J*, sodium hypochlorite (100 ppm available chlorine) (will corrode metal instruments); *K*, phenolic germicidal detergent solution (follow the product label for use-dilution); *L*, iodophor germicidal detergent solution (follow the product label for use-dilution); *M*, quaternary ammonium germicidal detergent solution (follow the product label for use-dilution).

<sup>†</sup> The longer the exposure to a disinfectant, the more likely it is that all micro-organisms will be eliminated. Ten minutes' exposure may not be adequate to disinfect many objects, especially those that are difficult to clean because they have narrow channels or other areas that can harbor organic material and bacteria. Twenty minutes' exposure may be the minimum time needed to reliably kill *M. tuberculosis* with glutaraldehyde.

<sup>‡</sup> Tubing must be completely filled for disinfection; care must be taken to avoid entrapment of air bubbles during immersion.

<sup>§</sup> Thermostability should be investigated when indicated.

<sup>||</sup> Do not mix rectal and oral thermometers at any stage of handling or processing.

<sup>¶</sup> Pasteurization (washer disinfectant) of respiratory therapy and anesthesia equipment is a recognized alternative to high-level disinfection.

Some data challenge the efficacy of some pasteurization units.

From Rutala WA: Draft guideline for selection and use of disinfectants. Am J Infect Control 17:24A, 1989; with permission.

**Table 2.** *Inactivation of Hepatitis B Virus and Human Immunodeficiency Viruses by Disinfectants*

| DISINFECTANT           | CONCENTRATION<br>INACTIVATING 10 <sup>6</sup> HBV,<br>10 MIN, 20°C | CONCENTRATION<br>INACTIVATING 10 <sup>5</sup> HIV,<br>≤10 MIN, 25°C |
|------------------------|--------------------------------------------------------------------|---------------------------------------------------------------------|
| Chlorine dioxide       | ND                                                                 | ND*                                                                 |
| Ethyl alcohol          | ND                                                                 | 50%                                                                 |
| Formalin               | ND                                                                 | ND*                                                                 |
| Glutaraldehyde         | 2%                                                                 | ND*                                                                 |
| Glutaraldehyde-phenate | 0.13% glutaraldehyde-<br>0.44% phenate                             | ND                                                                  |
| Hydrogen peroxide      | ND                                                                 | 0.3%                                                                |
| Iodophor               | 80 ppm                                                             | ND*                                                                 |
| Isopropyl alcohol      | 70%                                                                | 35%                                                                 |
| Paraformaldehyde       | ND                                                                 | 0.5%                                                                |
| Phenolic               | ND                                                                 | 0.5%                                                                |
| Quaternary ammonium    | ND                                                                 | ND*                                                                 |
| Sodium hypochlorite    | 500 ppm                                                            | 50 ppm                                                              |

\* Some investigators have used reverse transcriptase activity and/or virus infectivity assays to determine the activity of other disinfectants against HIV. Other disinfectants that inactivate HIV include 1:200 dilution of chlorine dioxide; 1 per cent formalin; 0.25 per cent iodophor; 0.08 per cent quaternary ammonium compound; and glutaraldehyde.

Abbreviation: ND, no data.

From Rutula WA: Draft guideline for selection and use of disinfectants. *Am J Infect Control* 17:24A, 1989; with permission.

infection is adequate, infections are not being transmitted to patients, and that the function and integrity of the product are not compromised.

### Decontaminating Spills of Blood and Body Fluids

Spills of blood or body fluids on equipment or environmental surfaces should be cleaned and decontaminated as soon as practically feasible. Visible material should be removed with soap and water followed by decontamination using hospital disinfectants that are classified as tuberculocidal. Gloves should be worn during these procedures.

Horizontal surfaces of anesthesia equipment and work surfaces should be wiped between cases and at the conclusion of the work day. Vertical surfaces should be terminally cleaned or more often if there is an obvious contamination with blood or body fluids.

### Other Infection Control Considerations

Universal precautions are recommendations for preventing transmission of blood-borne pathogens but are inadequate to control the spread of other forms of infections. The institution of universal precautions does not preclude the use of other infection control techniques necessary to prevent the spread of diseases through other routes such as respiratory or fecal-oral. Many highly contagious pathogens such as tuberculosis may be transmitted through the respiratory

Table 3. Some Common Disinfectants with Their Use Dilutions, Properties, and Cost

| INACTIVATES*          |                               | IMPORTANT CHARACTERISTICS     |                    |                   |                 |                |                  |                     |           |         |               | APPROXIMATE COST (IN DOLLARS) |                      |       |                   |                     |                              |
|-----------------------|-------------------------------|-------------------------------|--------------------|-------------------|-----------------|----------------|------------------|---------------------|-----------|---------|---------------|-------------------------------|----------------------|-------|-------------------|---------------------|------------------------------|
|                       |                               | Inactivated by organic matter |                    |                   |                 |                |                  |                     |           |         |               |                               |                      |       |                   |                     |                              |
|                       |                               | Bacteria                      | Lipophilic viruses | Hydrophilic virus | M. tuberculosis | Mycotic agents | Bacterial spores | Shelf life > 1 week | Corrosive | Residue | Skin irritant | Eye irritant                  | Respiratory irritant | Toxic | Easily obtainable | Purchase/legal      | Cost per gal at use-dilution |
| USE DILUTION (ACTIVE) | DISINFECTANTS                 |                               |                    |                   |                 |                |                  |                     |           |         |               |                               |                      |       |                   |                     |                              |
| 60-95% Low            | Isopropyl alcohol             | +                             | +                  | -                 | +               | +              | -                | +                   | -         | +       | +             | +                             | -                    | +     | +                 | 3.75 (70%)          | 3.75 (70%)                   |
| 3-25% CS/high         | Hydrogen peroxide             | +                             | +                  | +                 | +               | +              | +                | +                   | +         | -       | +             | +                             | -                    | +     | +                 | 2.37 (3%)           | 2.37 (3%)                    |
| 3-8% High             | Formaldehyde                  | +                             | +                  | +                 | +               | +              | -                | +                   | -         | +       | +             | +                             | +                    | +     | +                 | 7.94 (37% wt)       | 0.79 (3.7% wt)               |
| 500-2500 ppm Low      | Quaternary ammonium compounds | +                             | +                  | -                 | -               | ±              | -                | +                   | -         | +       | +             | +                             | -                    | +     | +                 | 8.60-14.40 (37% wt) | 0.06 (0.4%)                  |
| 700-2500 ppm Low      | Phenolic                      | +                             | +                  | ±                 | ±               | ±              | -                | +                   | +         | -       | +             | +                             | -                    | +     | +                 | 8.20-13.90 (0.4%)   | 0.03(0.4%)                   |
| 100-1000 ppm High/low | Chlorine                      | +                             | +                  | +                 | +               | +              | -                | +                   | +         | +       | +             | +                             | +                    | +     | +                 | 0.70 (5.25%)        | 0.07 (0.5%)                  |
| 30-50 ppm Low         | Idophors                      | +                             | +                  | +                 | ±               | ±              | -                | +                   | +         | +       | +             | +                             | -                    | +     | +                 | 12.80 (10%)         | 0.128 (0.1%)                 |
| 2% CS/high            | Glutaraldehyde                | +                             | +                  | +                 | +               | +              | +                | +                   | -         | +       | +             | +                             | -                    | +     | +                 | 8.50-11.00          | 8.50-11.00                   |

\* Inactivates all indicated micro-organisms with a contact time of 30 minutes or less, except bacterial spores, which require 6 to 10 hours contact time. Abbreviations: CS, chemosterilizer; +, yes; -, no; ±, variable.  
 From Rutala WA: Draft guideline for selection and use of disinfectants. Am J Infect Control 17:24A, 1989, with permission.

route and appropriate precautions such as the use of masks must be instituted when dealing with patients who are known carriers.<sup>28</sup>

## EMPLOYER'S RESPONSIBILITIES

To comply with OSHA's proposals relating to blood-borne infections, employers of health care workers should establish written infection control plans that are designed to minimize or eliminate exposure to pathogens.<sup>11</sup> As the initial step in this process, employers should identify tasks and procedures in which occupational exposures may occur and categorize the employees into groups based on the occupational risk of blood-borne exposure.<sup>10</sup> Category I tasks involve exposure to blood, body fluids, or tissues. Category II tasks involve no exposure to blood, body fluids, or tissues, but employment may require performing unplanned category I tasks. Category III tasks involve no exposure to blood, body fluids, or tissues, and category I tasks are not a condition of employment.

Anesthesiologists and anesthesiologists would routinely perform category I tasks. Employees who normally stock equipment and usually have no exposure to blood or body fluids would fall into category II if they might contact used equipment or be asked to transport blood samples. A secretary or an individual in an administrative position would perform category III tasks.

Employers must provide protective equipment such as gloves and eye wear for employees who perform category I tasks and make individuals who perform category II tasks aware of the location and proper use of such equipment. Protective equipment must be of appropriate sizes and be located in proximity to the areas of anticipated use. There should be programs to assure that equipment is working properly and in designated locations.

An initial orientation program and continuing education must be provided to train health care workers on current infection control practices, the mode of transmission and prevention of blood-borne infections, and the need for routine use of universal precautions. Employers should also monitor employees to be sure that they are adhering to recommended practices and procedures. If employees fail to follow the recommended precautions, counseling and education and retraining should be provided and, if necessary, appropriate disciplinary measures should be considered.

### Hepatitis B Vaccination

Employers should make hepatitis B vaccination available to all employees who are at risk for contact with blood or body fluids, unless the employee has previously been vaccinated or immunity can be demonstrated. Employees may choose to be tested for hepatitis B surface antibody prior to vaccination. The employer should record dates of vaccination and testing or document that the health care worker has declined vaccination.

### Post-Exposure Evaluation

A confidential medical evaluation and follow-up should occur if a health care worker has a parenteral or mucous membrane exposure to blood or body fluids. The incident should be documented, and the patient source of the blood or body fluid should be determined if possible. If permission from the patient can be obtained, they should be tested for HIV and HBV infection. The health care worker should be tested to determine their initial HBV immunity status and for antibodies to HIV. The medical condition of the health care worker should be followed and repeat serologic testing performed based on current recommendations of the CDC.<sup>4, 11</sup> For individuals exposed to HBV, hepatitis B vaccine, or hepatitis B immune globulin may be required based on the antibody status and history of previous vaccination.<sup>8, 20</sup> (See article in this issue on Viral Hepatitis for specific recommendations.)

### THE HEALTH CARE WORKER WITH HBV OR HIV INFECTIONS

Transmission of hepatitis B from health care workers to patients has occurred but with extremely low frequency and is usually associated with breaks in infection control techniques. In a prospective study of nine health care workers positive for hepatitis B surface antigen, it was determined that the risk of transmission of the disease to patients was very small.<sup>21</sup> Galambos<sup>14</sup> has reviewed this topic and suggests that the risk can only be estimated based on prospective studies and investigations of specific incidents. He recommends that health care workers avoid patient contact during the acute phase of hepatitis B. Chronic carriers should strictly adhere to infection control techniques including the routine use of gloves.

Several studies have documented that HIV is not transmitted through casual contact.<sup>13, 25</sup> When infection control procedures are closely followed, it is unlikely that health care workers with HIV infection would transmit the virus to patients. However, health care workers with HIV infection may be at increased risk of acquiring and having serious complications from infectious diseases if their immune mechanisms are impaired. Health care workers with altered immunity should be counseled about the potential risk of caring for patients with infections.<sup>4</sup> Because HIV infection may impair the health care worker's physical or mental abilities, these must be evaluated by their personal physician and a determination made in conjunction with the medical director and personnel health service of the hospital as to whether they can safely be allowed to perform patient care activities.<sup>4</sup>

### SUMMARY

During the past decade, health care workers have become more aware of the risk of occupational transmission of infections as a result

of the AIDS epidemic. Although the risk of occupationally transmitted HIV infection appears to be very low for health care workers, there is a renewed interest in infection control techniques. The Federal government through OSHA is now proposing practice standards to prevent transmission of blood-borne infections in the workplace. Anesthesia departments must respond by implementing infection control plans to protect anesthesia personnel and patients from infections. Vaccination can provide immunity to HBV, and universal precautions must be implemented to prevent occupational-acquired infection from other blood-borne pathogens. Recommendations have been made concerning the employment of health care workers with HBV and HIV infections.

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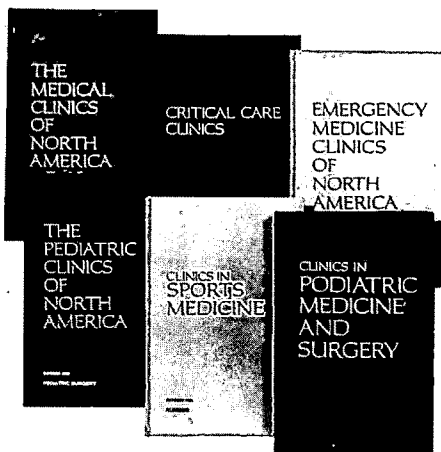
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